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VOLUME IX NUMBER 4

APRIL, 1920

STUDIES FROM THE DEPARTMENT OF MEDICINE

Including

Pediatrics and Dermatology

1914/19

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477 FIRST AVENUE
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THE TOTAL ENERGY REQUIREMENT IN DISEASE

AS DETERMINED BY CALORIMETRIC OBSERVATIONS*

EUGENE F. DU BOIS, M.D.
NEW YORK

The total energy requirement of an individual is represented by his heat production or, in other words, his total metabolism. If food of a total caloric value equaling the heat production be taken, the normal man will remain in nutritive balance. As a rule, the appetite in health regulates the intake to a nicety, although some of us need the guiding influence of the bathroom scales and the restraining influence of tight clothes. In disease, on the other hand, the appetite is no index of the requirement and the nutrition of the cells is at the mercy of the physician. Likewise, the stomach and kidneys are at his mercy, and he must regulate the diet so that it will nourish the cells without throwing too much work on damaged organs or oxidative functions of the body. It is often just as important to know the proper dosage of foods as to know the proper dosage of drugs.

The most satisfactory instrument for measuring the heat production is the respiration calorimeter[1] of the type devised by Atwater and Rosa in Middletown, Connecticut. Such a calorimeter, modified for clinical purposes, has been constructed by the Russell Sage Institute of Pathology in the wards of the Second Medical Division of Bellevue Hospital. Since its completion a year and a half ago, it has been used in 142 observations. A number of normal controls have been studied, but most of the subjects have been patients from the adjoining metabolism ward in which all diets are weighed and analyzed. This ward is under the

* Read before the Section on Practice of Medicine and the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914.

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Atwater and Rosa: Description of a New Respiration Calorimeter, 1899, Bull. 63, U. S. Dept. of Agr. Benedict and Carpenter: Respiration Calorimeter for Studying the Respiratory Exchange and Energy Transformations of Man. Carnegie Instit. Wash., 1910, Pub. 123.

control of the institute and those in charge of the calorimeter.

On the morning of the observation a patient, usually without his breakfast, is placed within the calorimeter where he remains for three or four hours. He finds himself on a comfortable bed in a well-ventilated box about the size of the lower berth of a sleeping-car. He can amuse himself by looking out of the windows, but since the scenery is monotonous he usually dozes for about half the time and allows his mind to vegetate for the other half. Absolute rest is essential, and the only movements permitted are those connected with turning in bed from time to time. All such movements are registered automatically by a device which is delicate enough to record even the small amount of work done by a man in stroking his mustache.

As the subject lies in the calorimeter the oxidation of the various foodstuffs within his tissues produces a certain amount of heat each hour. Approximately three-fourths of this heat leaves the surface of the body by means of radiation and conduction. This heat is removed from the calorimeter by a system of cooling pipes and is accurately measured by electrical thermometers. About one-fourth of the heat is removed from the body by the vaporization of water from skin and lungs. This water vapor is caught and measured in a sulphuric acid bottle.

If the body temperature should rise, it is obvious that some of the heat produced would be stored in the body itself and not eliminated. The estimation of this heat in short periods is a matter of great technical difficulty since the changes in rectal temperature, which are recorded every four minutes by means of a very accurate electrical thermometer, may not represent the average temperature changes of the body. Other thermometers strapped in the axillae and on the surface of the thorax or abdomen demonstrate that the different parts of the body show temperature curves which are by no means parallel, and that one part of the body may even be cooling while another part is warming. If the body temperature of a man of average size rises 0.5 degree centigrade it means that from 25 to 30 calories have been stored in the body in addition to the calories eliminated from the body. Such large changes, amounting to one-fourth or one-third of the total heat production for an hour,

have been observed within an hour, and it is obvious that any inaccuracy in the determination of the average body temperature causes an error in the method of direct calorimetry. While the error may be large in a single hourly period, it becomes very small in an observation lasting three or four hours and seldom exceeds 5 per cent.

The heat production is measured not only by this method of direct calorimetry but also by the more accurate method of indirect calorimetry. The box is ventilated by a rotary fan which sucks the air out of one end of the chamber, drives it through a bottle of

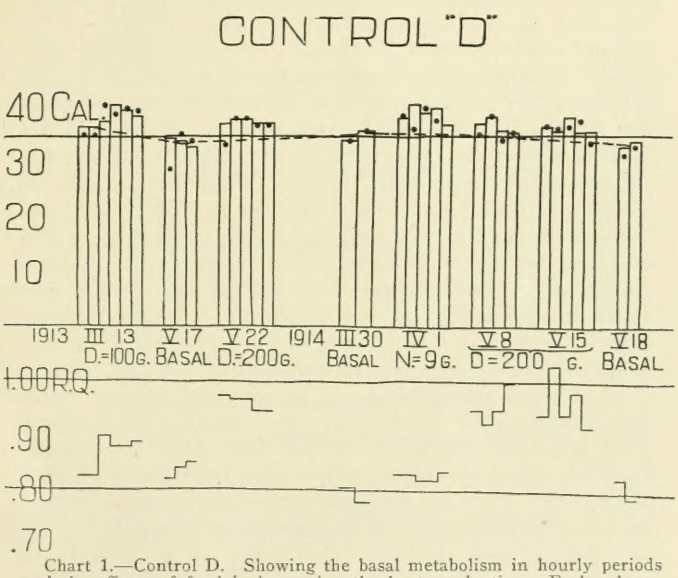

Chart 1.—Control D. Showing the basal metabolism in hourly periods and the effects of food in increasing the heat production. Each column represents the calories per square meter of body surface as determined by the method of indirect calorimetry. The round dot represents the calories as measured by the method of direct calorimetry. *D* stands for glucose; *N*, nitrogen in the form of casein and egg albumin. These were taken approximately one hour before start of observation except on March 13, 1913, when the glucose was taken after the basal metabolism had been determined in two one-hour periods.

sulphuric acid to remove all moisture, then through a bottle of soda lime to remove the carbon dioxid and finally returns the same air, absolutely pure and odorless, to the other end of the calorimeter. As the patient uses up oxygen, this gas is supplied automatically from a small tank. By weighing these various

bottles and tanks at the beginning and end of each hour it is a simple matter to determine the carbon dioxid produced and the oxygen consumed. Knowing the relative proportions of these and also the nitrogen of the urine one is able to calculate with great accuracy the grams of protein, fat and carbohydrate oxidized by the patient during that hour. Knowing the heat produced by the oxidation of 1 gm. of each of these substances it becomes a simple matter to calculate the total heat production.

The two methods of direct and indirect calorimetry agree within 5 per cent. in about three-fourths of the experiments, and in many cases the figures are almost identical as is shown in Chart 1, that of one of the normal controls. In the total of all the experiments so far calculated, involving the measurement of 23,000 calories, the two methods agree within 1.6 per cent. As yet no disease has been found in our somewhat limited series of observations in which there is any consistent disagreement between the two methods. This is a matter of considerable import, since the previous work in the study of the heat production in disease has been done almost exclusively by the method of indirect calorimetry. The agreement of the two methods shows that the calculations by indirect calorimetry have not been vitiated by any profound and unsuspected changes in the intermediary metabolism.

It is comparatively easy to determine the total metabolism but difficult to find the exact normal figure with which to compare the results. We have measured the basal heat-production of a number of normal persons of varying weights and have grouped them with the normal controls examined by Benedict in his bed calorimeter, all determinations being made on individuals at complete rest, from fourteen to sixteen hours after the last meal. It will be seen in Chart 2 that if we express the metabolism in terms of calories per square meters of the body surface per hour, the results will group themselves close to the average figure of 34.2 irrespective of the body-weight. The dotted line represents the average of forty-nine normal controls studied by various types of apparatus in many laboratories. It is evident that the level is the same for persons whose weights are between 40 and 50 kg. (from 88 to 110 pounds) as for those whose weights are between 60 and 70 kg. (from 132 to 154 pounds).

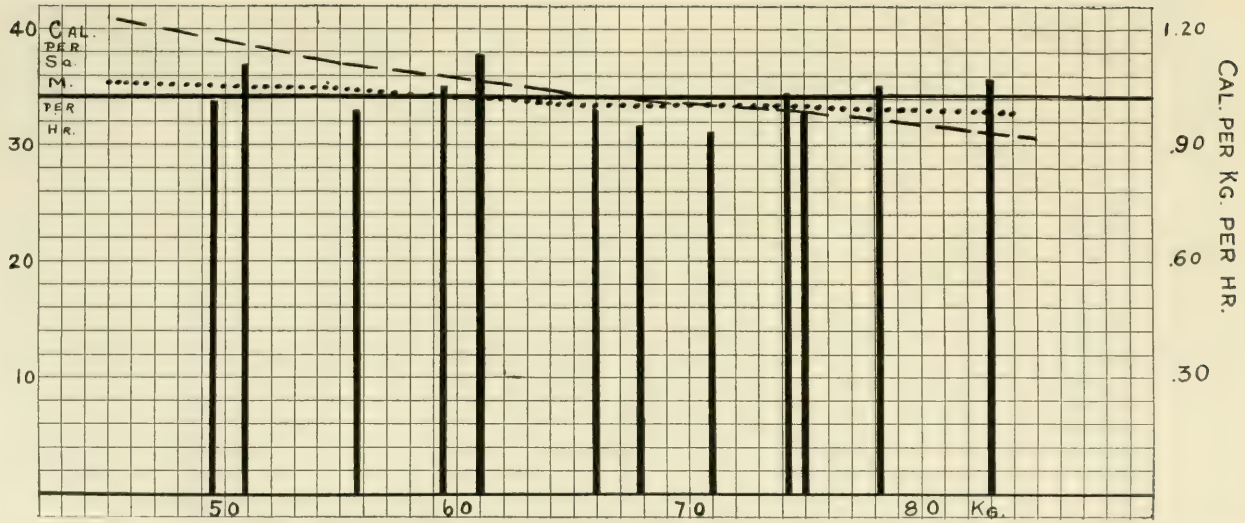

Chart 2.—Basal metabolism of normal men from fourteen to sixteen hours after the last meal. Columns represent calories per square meter per hour produced by subjects in bed calorimeter. Horizontal line drawn at 34.2, the average. Interrupted lines represent averages of 49 normal controls studied with various types of respiration apparatus, arranged in five groups according to weight. Dotted line shows the results expressed according to surface area. Dash line represents the same 49 controls with the results expressed in terms of calories per kilogram per day.

On the other hand, if we express the results in terms of calories per kilogram per day we have a line of averages which falls steadily as the weight increases. In order to have a single base-line which need not be changed for persons of varying weights we therefore compare all our results with the average normal figure of 34.2 calories per square meter per hour.

While the metabolism of a given individual remains fairly constant for years, there may be a variation among normal men of 10 per cent. above or 10 per cent. below the average. Further study will perhaps show even a greater variation. The metabolism is increased in childhood, diminished in old age, and probably depends, to a great extent, on the nutrition of the body and the mass of active protoplasm. Nevertheless, Rubner's law that the metabolism of different individuals and different species of animals is proportional to surface area does hold good within certain limits. These limits may be wide when we try to compare the metabolism of babies, guinea-pigs, athletes and fat men, but, as we have shown above, the limits are narrow for a group of men of approximately normal build.

Voit and Rubner demonstrated the fact that the taking of food raised the heat production, and the term of specific dynamic action was applied to this phenomenon. The cause of this was little understood until Lusk[2] studied the matter in great detail, making hourly determination of the heat production of dogs in the small Cornell calorimeter. His work on dogs has been duplicated on normal men as nearly as the human stomach will permit, but, of necessity, the amounts of food are relatively smaller and the increases in heat production distinctly less marked. Chart 1 shows the basal metabolism of control D and the effects of glucose and protein meals. The increase after glucose amounts to from 8 to 10 per cent. and after protein to 12 per cent.

Since the time of Voit and Pettenkofer a great deal of work has been done on the subject of the respiratory metabolism and total heat production in disease. Magnus-Levy[3] established the fact that in exophthal-

2. Lusk: Animal Calorimetry, Papers II, III, V, VI, Jour. Biol. Chem., 1912, xii, 349; xiii, 27, 155, 185; Cause of the Specific Dynamic Action of Protein, Arch. Int. Med., December, 1913, p. 485; The Specific Dynamic Action of the Foodstuffs, this issue, p. 824.

3. Magnus-Levy: Gaswechsel bei Thyroiden, Berl. klin. Wchnschr., 1895, xxxii, 650; Ueber Myxödema, Ztschr. f. klin. Med., 1904, lii, 201.

mic goiter the energy requirement was greatly increased even to a point as high as from 50 to 70 per cent. above the normal and showed that in cretinism and myxedema the heat production might be as low as from 45 to 50 per cent. below the normal. Kraus,[4] Grafe,[5] Rolly[6] and others demonstrated that in typhoid

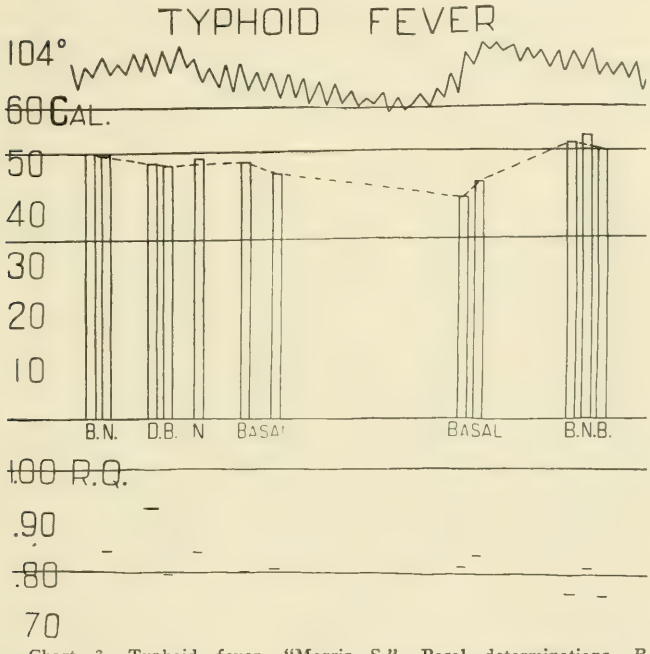

Chart 3.—Typhoid fever, "Morris S." Basal determinations, *B* connected by dash line. *N*, protein meal. *D*, from 100 to 200 gm. of glucose. Results expressed in averages.

fever the metabolism was raised to from 30 to 40 per cent. above the normal. Grafe[7] has recently shown that the heat production is low in certain stuporous

4. Kraus, Fr.: Ueber den respiratorischen Gasaustausch im Fieber, Ztschr. f. klin. Med., 1890, xvi, 160.

5. Grafe: Untersuchungen über den Stoff- und Kraftwechsel im Fieber, Deutsch. Arch. f. klin. Med., 1911, ci, 209.

6. Rolly: Experimentelle Untersuchungen über den Stoffwechsel im Fieber und in der Rekonvalescenz, Deutsch. Arch. f. klin. Med., 1911, ciii, 93.

7. Grafe: Beiträge zur Kenntniss der Stoffwechselverlangsamung bei stuprösen Zuständen, Deutsch. Arch. f. klin. Med., 1911, cii, 15; Die Steigerung des Stoffwechsels bei chronische Leukaemie und ihre Ursachen, Deutsch. Arch. f. klin. Med., 1911, cii, 406; Das Verhalten von Gesamtstoffwechsel und Eiweissumsatz bei Karzinomatösen, Deutsch. med. Wchnschr., 1914, xl, 518.

conditions and increased in lymphatic leukemia and cancer. The total heat production in diabetes has been studied by many observers with varying results, but Benedict and Joslin,[8] using the calorimeters in Boston, have shown that in cases of severe diabetes with acidosis there is an increase in metabolism.

The study of the metabolism in typhoid fever and the effects of the high-calory diet was begun in Bellevue Hospital in 1911 in association with Dr. Warren Coleman. The small Benedict apparatus was used and the calculations were made according to the method

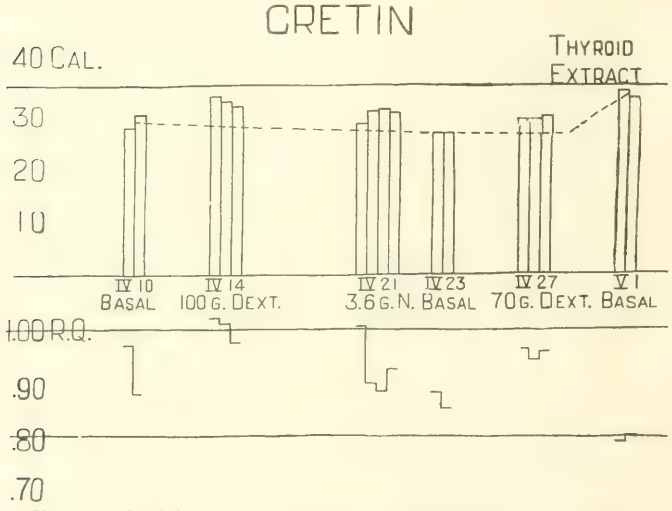

Chart 4.—Cretinism results expressed in hourly periods. Thyroid-extract treatment begun two days before last observation.

of indirect calorimetry. A summary of the results will be presented by Dr. Coleman[9] in another Section but it may be stated that the heat production of the patients was not raised by the administration of large amounts of food during the height of the fever. The matter seemed so important that it demanded investigation by the use of the calorimeter.

8. Benedict and Joslin: Metabolism in Diabetes Mellitus, Carnegie Inst. Wash., 1910, Pub. 136; A Study of Metabolism in Severe Diabetes, 1912, ibid, Pub. No. 176.

9. Coleman, W.: The Effects of Food on Metabolism in Typhoid Fever, read in the Section on Pharmacology and Therapeutics at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914.

Observations were therefore made on nine typhoid patients during the course of the fever and convalescence. The first part of the results on one patient, who was in the calorimeter twenty-two times, is shown in Chart 3. This patient enjoyed the work with the calorimeter. His original infection was by no means mild and he had one relapse which was severe and a second relapse which scarcely interrupted a rapid convalescence. Throughout the disease he was so well nourished that his weight remained practically constant.

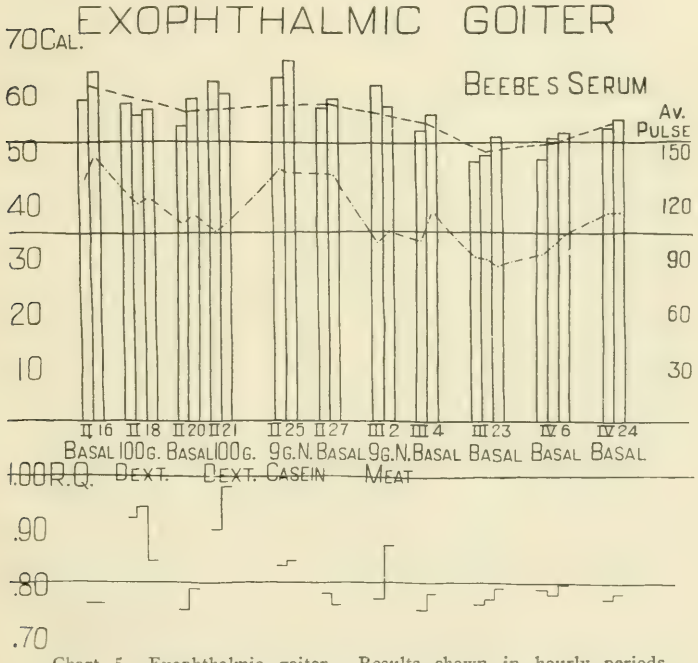

Chart 5.—Exophthalmic goiter. Results shown in hourly periods. Dash line connects basal determinations. Dot-dash line represents average pulse during the period of observation in calorimeter.

It will be noticed that during the fever his total metabolism was from 40 to 50 per cent. above the average normal and that it was scarcely increased at all on the days when the observations were made shortly after the ingestion of 100 gm. of glucose or 64 gm. of protein. A study of the nitrogen in the urine in this and three other cases shows that the percentage of calories derived from protein during fever

when the patients were fasting was seldom raised above the upper normal limit of 20 per cent., although one patient early in his disease derived 28 per cent. of the calories from protein.

As the temperature falls the total metabolism diminishes and the percentage of calories derived from protein drops to 10 or 15 per cent. During convalescence heat production may be from 20 to 30 per cent. above normal, and at this stage glucose and protein exert as great a specific dynamic action as in health.

The diseases of the thyroid gland have been studied with particular interest since the level of the total metabolism seems to be the best index of the activity of the thyroid secretion. In one cretin who was 36 years old but had the mental and physical development of a child of 8, the total energy requirement was from 18 to 25 per cent. above the normal but was raised almost to the normal on the third day of treatment with thyroid extract (Chart 4). The specific dynamic action of food was normal in this patient.

A series of seven patients with exophthalmic goiter were studied before and after treatment in an effort to guide the therapeusis in this disease, which is remarkable for the number of "remedies" that do not give relief. Luckily we were able to show some beneficial effects of treatment, although good results were obtained by rest and careful feeding alone. One patient, who had shown moderately severe symptoms for one year, was studied over a considerable period of time. If we look at the results as expressed in Chart 5, we notice that, in marked contrast to the cretin, the metabolism is 80 per cent. above the normal, falling to 60 per cent. on rest and good food. Von Noorden[10] has stated that the specific dynamic action of food and especially of meat is increased in fever and in exophthalmic goiter. We have seen that this was not the case in fever and it was evidently not true of this patient, since his metabolism was not raised even so much as that of a normal man by glucose, casein and meat. After treatment by Dr. S. P. Beebe with his antithyroid serum, there was a distinct improvement in the man's condition and fall in the metabolism. After the first month there was a rise

10. Von Noorden: New Aspects of Diabetes, New York, E. B. Treat & Co., 1912, p. 20.

in metabolism to its former level but the general improvement continued perhaps, however, at a slower rate.

A young woman who was up and about, though not quite able to continue her work as trained nurse, showed the extraordinarily high metabolism of 92 per cent. above the normal. After ligation of the arteries by Dr. John Rogers, the metabolism fell to 60 per cent. above the normal and the patient's condition was distinctly improved.

One young woman with a mild case of the disease showed a marked rise in metabolism four days after ligation of the four thyroid arteries, indicating that the operative procedure had temporarily increased the activity of the gland. Later there was distinct improvement in her general condition and a fall in the heat production to its former level.

Other conditions have been studied in a few cases and while the results need confirmation, they are suggestive and may lead to a better understanding of the various factors which influence the heat production in disease. One patient with splenic anemia, whose hemoglobin was 25 per cent., had a metabolism 11 per cent. above the normal; another with pernicious anemia for which a splenectomy had been performed, showed an increased metabolism amounting to 20 and 26 per cent. above the normal, while his hemoglobin was only 20 per cent. This confirms the older work, which demonstrated that there is no diminution of oxidation as a result of the low percentage of hemoglobin. In a patient with nephritis a change in blood-pressure from 195 to 160 caused absolutely no change in heat production. One man with acromegaly had a metabolism 18 per cent. above the normal, another with symptoms of deficiency of the secretion of the posterior lobe of the hypophysis gave results sometimes high and sometimes normal but he was so stupid that he made a very unsatisfactory subject. Another man with malaria was studied at the height of his fever, and also six days later when his attacks were cured. With a temperature of 104 F. the metabolism was 83 per cent. above the average, with a normal temperature of 21 per cent. A patient with auricular fibrillation, mitral stenosis and greatly enlarged heart but without orthopnea, was observed three times lying flat on his back and twice propped up with a back-rest. We were

astonished to find the metabolism which was normal when he was propped up was 8.5 per cent. higher when he was lying down and were even more surprised to observe the same phenomenon in the only normal control we studied in this posture.

The increases due to fever, hyperthyroidism and the like, are probably small compared to the increase caused by muscular work in delirium tremens or convulsions. Even slight restlessness or mild excitement causes a rise in heat production which is distinctly appreciable in the calorimeter.

In conclusion, it may be well to emphasize the fact that the nutrition of a patient depends absolutely on the relationship between his energy production and his food-supply. If the organism fails to obtain food from without it will draw on its own glycogen stores, fat depots and supplies of body protein.

129 East Seventy-Sixth Street.

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CLINIC OF DR. EUGENE F. DuBOIS

CORNELL UNIVERSITY MEDICAL SCHOOL

THE BASAL METABOLISM AS A GUIDE IN THE DIAGNOSIS AND TREATMENT OF THYROID DISEASE[1]

IT is an easy matter to make a diagnosis in a typical case of hyperthyroidism presenting the cardinal symptoms of goiter, exophthalmos, tremor, and rapid pulse. Even a layman can tell what the trouble is at a glance if he has ever had a friend with Graves' disease. Typical cretinism can be diagnosed by anyone who has traveled in the Alps. In marked contrast to these extremes there is a large group in which it is most difficult to decide whether or not the patient is suffering from increased or decreased activity of the thyroid gland. These are the very cases in which a correct diagnosis is most important because of the good results that can be obtained by proper treatment.

Scores of tests have been presented as an aid in confirming the diagnosis of exophthalmic goiter. There is only one that stands out as a rational measure of the degree of hyperthyroidism, and that is the measurement of the basal metabolism. Since this is a matter of some complexity it may be well to discuss it before presenting the individual patients studied by this method.

The basal metabolism of a man is represented by the number of calories he produces in the morning hours, before breakfast while resting quietly in bed. Usually this is expressed in terms of calories per hour per square meter of body surface. The study of a large number of normal men and women has shown that the level of the basal metabolism varies with the age, sex,

[1] A series of cases in the metabolism ward of the Russell Sage Institute of Pathology in Bellevue Hospital presented to the students of Cornell University Medical College.

and surface area of the individual. Just why the metabolism should be proportional to the surface area is not clear, but the fact seems well established and is of great convenience in expressing the normal standards. Once having determined a man's heat production and having estimated his surface area from his height and weight, it is easy to compare the result with the normal standard for his age and state that his basal metabolism is such and such a percentage above or below the normal average. There are comparatively few normal individuals whose basal figures are more than 10 per cent. above or below the average. Practically all come within the 15 per cent. limit.[1]

A few years ago the measurement of the heat production was a difficult matter, attempted in only a few laboratories and clinics. At the present time there are half a dozen hospitals in this country where these tests are being made, especially on patients with exophthalmic goiter. In most places one of the simpler forms of apparatus is used, such as the Benedict universal respiration apparatus or the Tissot spirometer.[2] These measure the oxygen consumption in periods of ten to fifteen minutes, allowing one to calculate the heat production by the method of indirect calorimetry. Much more complicated is the large respiration calorimeter, such as was used in the study of the patients here presented.

As might be expected, there are several diseases which cause an increase in the basal metabolism. Patients with high fever

[1] Lusk, The Elements of the Science of Nutrition, 3d ed., Phila., 1917, W. B. Saunders Co.

Gephart, F. C., and DuBois, E. F., Clinical Calorimetry, Paper IV, The Determination of the Basal Metabolism and the Effect of Food, Arch. Int. Med., 1915, xv, 835.

DuBois, D., and DuBois, E. F., Clin. Cal., Paper X, A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Ibid., 1916, xvii, 863.

Aub, J. C., and DuBois, E. F., Clin. Cal., Paper XIX, The Basal Metabolism of Old Men, Ibid., 1917, xix, 823.

[2] Carpenter, T. M., A Comparison of Methods for Determining the Respiratory Exchange of Man, Carnegie Institution of Washington, Publication No. 216, Washington, 1915.

Benedict, F. G., A Portable Respiration Apparatus for Clinical Use, Boston Med. and Surg. Jour., 1918, clxxviii, 667.

are 30 to 40 per cent. higher than normal. In severe cardiac and renal disease and anemia the results may be high, and in leukemias with very large numbers of white cells the heat production may be almost double the normal. Some patients with acromegaly give high results.

Fortunately, most of these conditions are easily diagnosed and are seldom confused with thyroid disease. It is in hyperthyroidism that we find the highest basal metabolism, and there is a striking parallelism between the severity of the disease and the level of the heat production. In very severe cases the increase is more than 75 per cent., in severe cases 50 to 75 per cent., and in moderately severe and mild cases less than 50 per cent. Conversely, in cretinism and myxedema the metabolism may be 20 to 40 per cent. below the normal average, figures lower than in any other condition except profound emaciation. In such cases of deficient thyroid secretion the metabolism can be raised by the proper administration of thyroid extract.

An increased basal metabolism is not pathognomonic of hyperthyroidism any more than sugar in the urine is pathognomonic of diabetes. In fact, there is a striking similarity between these leading manifestations of the two great diseases of metabolism—diabetes and hyperthyroidism. If a patient complains of polyuria, polydipsia, and loss of weight and strength in spite of an increased appetite, we suspect that there is some interference with the oxidation of the carbohydrates, and confirm the diagnosis by testing the urine for sugar. If another patient gives a history of mental irritability, rapid, throbbing heart action, warm, sweating skin, increased appetite, and loss of weight we recognize that these are the symptoms of increased metabolism, and if fortunate enough to have the means at our disposal we confirm the diagnosis of hyperthyroidism by measuring the heat production. In this manner it may be possible to diagnose "exophthalmic goiter" without waiting for the appearance of exophthalmos or goiter. In diabetes we gage the effect of treatment by determining how much carbohydrate can be oxidized. In hyperthyroidism we can follow the course of the disease by watching the fluctuations in the basal metabolism.

The first patient is Anna K.,[1] referred to the metabolism ward by Dr. John Rogers. She is a nurse, twenty-six years old, of a rather neurotic family. At the age of sixteen she had rheumatic fever, and since then has been high strung and easily frightened. For several years she has suffered from dyspnea and palpitation on exertion, and about a year and a half ago these symptoms grew worse, and she began to have severe headaches, marked sweating of the skin, excessive appetite, and thirst. Two months ago she was badly frightened in a runaway and all the symptoms increased in severity. Since then she has been taking a special thyroid "residue" prepared at the Loomis Laboratory. On April 4th both superior thyroid arteries were ligated by Dr. Rogers in this hospital.

On April 28th, at the time of the first calorimeter observation, she presented the picture of extreme hyperthyroidism except that there was only slight exophthalmos and no lagging of the lids on looking downward. The expression was tired and neurotic, the eyelids were puffy, and the voice weak. The frame was small and she was very thin, weighing only 98 pounds, which was 15 less than her usual weight. The thyroid gland was moderately enlarged, especially on the right side. The tongue and hands were tremulous, the skin moist and warm. The cardiac impulse was diffuse, maximum in the fifth space, 8.5 cm. to the left of the midline. The action was regular, averaging 121 per minute.

The first hour that she was in the respiration calorimeter she produced 102.6 calories; the second hour, 101.5. According to her surface area this was 104 per cent. above the normal average. This means that every square inch of her skin was giving off twice as much heat as in the case of a normal woman, so it is no wonder that it felt warm and moist. Her food requirement was double the normal, and her emaciation showed that the intake had not increased correspondingly.

On April 29th, the day after this observation, Dr. Rogers

[1] The details of histories and laboratory findings have been published in Clinical Calorimetry, 14th Paper, Metabolism in Exophthalmic Goiter, Arch. Int. Med., 1916, xvii, 915.

ligated the two inferior thyroid arteries. She stood the operation well, and on May 13th returned for another test in the calorimeter, feeling less nervous and more ambitious. This time she produced an average of 84.2 calories per hour, which was 71 per cent. above the normal average for a woman of her weight. The pulse-rate had fallen to 100 per minute.

This case illustrates several points. It shows that there can be an extreme degree of hyperthyroidism with only slight exophthalmos and moderate enlargement of the thyroid. It indicates an improvement following ligation of the arteries, but demonstrates that the gland can be markedly overactive even though all four thyroid arteries have been tied.

The second patient, Benny London, is at the other end of the scale of thyroid activity. He is a cretin of the type that used to be so common in some of the villages of Switzerland and Northern Italy. He has been at the Children's Hospital on Randall's Island for the last twenty years, and it is believed that he is about thirty-six years old. His mental and physical development corresponds to that of a small boy of seven. After twenty years of schooling he has finally learned how to write his name. Attempts to transplant sheep's thyroid into the abdominal wall and pelvis of the kidney failed to produce any beneficial results, and apparently caused the formation of a renal calculus. He has had numerous courses of treatment with Parke, Davis & Co. thyroid extract, but on doses as small as ½ to 1 grain three times a day develops tachycardia, weakness, and often syncope.

Benny is only 3 feet, 7½ inches tall and he weighs 51 pounds. His face is broad, eyelids baggy, lips thick, nose broad, teeth widely spaced. No thyroid gland can be felt. There is a small umbilical hernia and there are pads of fat on either side of the neck and others just anterior to the axillæ. His genitals resemble those of a boy of seven and there are no male secondary sexual characteristics. The skin is very dry, harsh, inelastic, with fine branny desquamation. His Wassermann test is strongly positive, the urine contains much sterile pus, apparently due to the calculi in the pelves of the kidneys. The temperature is slightly subnormal and the pulse 64 to 80.

Two calorimeter observations thirteen days apart show a basal metabolism 17 and 22 per cent. below the normal adult figure as based on his surface area. This means that he produces about half as much heat as a normal seven-year-old boy of his size because normal children show a very high basal metabolism.

After three days of treatment with thyroid extract, 3 grains a day, his metabolism returned almost exactly to the normal average for adults, but the temperature rose to 100° F., pulse to 100, and he felt so limp and looked so miserable that it was necessary to discontinue the extract.

No more popular patient has ever been in the ward than this little cretin. He is docile, uniformly good natured, full of fun, and blessed with a most contagious grin. At first his favorite occupation was hunting for bugs with a flash light, but he was disappointed by the negative results in Bellevue Hospital. He is a natural clown, and his humor is of a type that might well have been popular with the medieval monarchs who used these cretins as court jesters.

Our third patient, Max W., has been most unpopular in the ward because he teases his neighbors—the cretin and a pituitary patient of slow mentality. His excitable disposition and quick thoughts and actions show the driving force of too much thyroid secretion.

Max is a Rumanian Hebrew, forty years old, and for some time has been a storekeeper in this city. Two years before he came to the hospital he was refused life insurance because he weighed 190 pounds. A year before his first calorimeter observation he received news that his brother had been murdered and was much excited for a week. The next month he began to suffer from nervousness, loss of weight, and a severe, unproductive cough. He was sent to the mountains with a diagnosis of tuberculosis, but did not improve. It was then found that his Wassermann reaction was positive, and he was treated with mercury, still without improvement. Next he went to Mount Sinai Hospital, where they made a diagnosis of exophthalmic goiter and started medical treatment. He was discharged from this and one other hospital on account of quarrels with the nurses and

staff. He vehemently refuses surgical treatment because he saw a patient die after a thyroid operation. On the whole, he seems to have a poor opinion of the medical profession.

The patient is tall, but weighs only 136 pounds. His skin is warm and slightly cyanotic. The expression is angry and the eyes are staring, with slight protrusion. Although the upper lid covers about 2 mm. of the cornea, it does not follow the eyeball when he looks downward. There is some weakness of convergence; he winks but seldom, and the forehead wrinkles but slightly. His thyroid gland is soft and moderately enlarged, especially the right lobe. When admitted to Bellevue the cardiac apex was in the fifth space, 11 cm. to the left of the midline, and the action was rapid, 108 to 142, with a marked irregularity of the respiratory type. At the apex was a soft systolic murmur. The urine showed traces of sugar and the Wassermann was strongly positive.

On Feb. 16th, five days after admission to the hospital, his basal metabolism was 75 per cent. above the average normal. Four days later it dropped to 60 per cent., but after a week rose to 65 per cent. above the average. On March 4th it had fallen again to 54 per cent. This shows the improvement that follows rest in bed without medication. After March 5th he was treated by Dr. Beebe, who gave him cytotoxic serum. The patient felt much better and did not even object to the local reactions, which at times were severe. The metabolism fell slightly, reaching 39 to 53 per cent. above the normal. A year later he returned to the ward, saying that he was much stronger and less excitable. He had gained 22 pounds in weight and had been able to work in his store. The goiter was a little smaller, the eye symptoms were unchanged, and the skin was still moist and warm. The heart was fibrillating and the apex was 13.3 cm. to the left of the midline. His metabolism was 45 per cent. above the average.

It has been stated that this patient's urine contained traces of sugar. He was by no means a diabetic, as is shown by the fact that his blood-sugar remained normal on a diet containing 200 to 300 grams of carbohydrate. Absolute proof of his ability to oxidize sugar was furnished by the calorimeter. After taking 100

grams of glucose his respiratory quotients showed that he was deriving 60 to 90 per cent. of his calories from carbohydrate combustion.

This case illustrates that a patient suffering from hyperthyroidism can have his troubles ascribed first to tuberculosis and next to syphilis. If his doctor had examined his urine he might have been treated for diabetes also. The calorimeter indicated that rest in bed caused his basal metabolism to fall from 75 per cent. above the normal average to 54 per cent. A year's treatment with serum was not able to cause a drop of more than 9 per cent.

Our fourth patient, Anna R., has been followed for two years. She was the first thyroid patient tested in the calorimeter. When first seen she was twenty-nine years old, unmarried, a saleswoman. Five years before this she had typhoid fever, and on recovery noticed a swelling of her neck. Since then she has suffered from tremor, palpitation, restlessness, and loss of weight, but has been able to work up to the time of admission. She thinks she has improved during the last two years, but says that her friends noticed that her eyes were staring about one year ago.

The patient is tall and thin, with distinct exophthalmos and von Graefe's and Stellwag's signs. The thyroid is moderately enlarged, there is a slight tremor of the tongue and hands. The heart is slightly enlarged, the pulse 84 to 88.

On May 10th her basal metabolism was 34 per cent. above the normal average. On May 12th, under local anesthesia, the left superior and right inferior thyroid arteries were ligated and the tip of the left upper pole removed. On the 16th the other two thyroid arteries were ligated and the right upper pole removed. For fear that she might suffer from a sudden diminution of thyroid secretion she was given $\frac{1}{2}$ grain of thyroid extract every four hours until May 18th. On the 20th her metabolism was higher than before the operation, registering 55 per cent. above the average. Eight days later it was 52 per cent. This shows that an operation can increase the activity of the thyroid gland.

After leaving the hospital she spent a couple of months in the

country and gained weight and strength. She was then able to go back to work. A year after her operation she returned for a calorimeter observation. The thyroid was still enlarged, she was still weak and nervous, but her general condition was somewhat improved. Her basal metabolism was exactly the same as at the time of her first test.

A week later she was married and did well until her husband lost his job and she had to start work again in the store. When she reported at the metabolism ward two years after the first observation she was very thin, extremely nervous, and tremulous. Her skin was moist and the pulse small and weak. Unfortunately, it was not possible to measure her metabolism, but it was undoubtedly increased as a result of her efforts to support herself and her husband.

The fifth patient, Mrs. S., is in comfortable circumstances, but her breakdown was hastened by overwork, just as in the case of the saleswoman. She has always been energetic and athletic, but about five years ago developed an unusual degree of activity and restlessness. This led her to play tennis violently, and she won many cups in tournaments. She devoted herself to charities until it was evident that she was becoming nervous, irritable, and short of breath on exertion. A severe unproductive cough coupled with loss of weight made the family doctor suspect tuberculosis, and he sent her to a consultant. No diagnosis was made until the patient's mother-in-law suggested that the trouble was exophthalmic goiter, since the expression of the eyes reminded her of a man she knew who was suffering from this disease. A flood of light came to the family doctor, who promptly discovered a slight tremor, distinct tachycardia, puffiness of the eyelids, and unusual brilliancy in the eyes. On questioning, the patient admitted that she slept with very few blankets even on cold nights, and that her skin was always warm. In spite of treatment the condition grew worse and the exophthalmos became distinct, although there was never a goiterous swelling. Ligation of both superior thyroid arteries was performed by Dr. John Rogers, and during the next few years there was a slow improvement. The exophthalmos persisted, but the slight thick-

ening of the skin and some of the mental symptoms suggested that there was possibly an exhaustion of the gland with threatened myxedema. In order to see if thyroid extract were indicated Dr. Rogers advised a test to determine the level of the basal metabolism. The calorimeter showed that the heat production was 20 per cent. above the normal level and that the gland was still in the stage of hypersecretion.

The sixth and last patient, Peter N., was a puzzler. He was considered to be a case of atypical exophthalmic goiter and was referred to the metabolism ward to see if an operation were advisable. He was twenty-three years old and 6 feet 2 inches in height. His father was 6 feet 4 inches. The patient grew fast between the ages of fifteen and eighteen and became weak and nervous, losing his temper easily. He suffered from headaches two or three times a week, and about a year ago his hands grew so tremulous that he had to give up his work as mechanic. Shortly after this he went to the Massachusetts General Hospital, where his respiratory metabolism was studied by Dr. J. H. Means and found to be within normal limits. The superior thyroid arteries were ligated by the surgeons, and since then the headaches have been rather less frequent, but he is not much stronger and he only sleeps two or three hours at night.

The young man is tall and thin, but there is no suggestion of acromegaly in his appearance and the x-ray shows that the sella turcica is normal in contour. His expression is anxious, but there are no eye symptoms. The thyroid is soft and slightly enlarged. The hands and feet are sweating and there is marked dermatographia. Cardiac dulness extends 12 cm. to the left of the midline and the electrocardiogram shows a slight respiratory arhythmia. The pulse-rate is only 71. There is a trace of sugar in the urine.

One observation in the calorimeter showed that his metabolism was 2 per cent. below the average; in other words, absolutely normal. This, together with the test made a year previously by Dr. Means, rules out hyperthyroidism. In the light of our present knowledge we might suspect that this is a case of neurocirculatory asthenia.

As we review the preceding cases from the purely clinical aspect we are struck by the importance of symptoms outside the classical group of exophthalmos, goiter, tremor, and tachycardia. As Plummer has pointed out, the earliest symptoms are cerebral stimulation, vasomotor disturbances of the skin, tremor, mental irritability, tachycardia, and loss of strength. In two of the cases we have noted that there was an irritative cough, which led the physician to suspect tuberculosis. Before there is distinct exophthalmos there is usually a peculiar look of the eyes, an unusual brilliance, a slightly startled, angry expression. There is also an impulsiveness of manner and distinct restlessness of disposition. Often the patients complain that they cannot get along with people and especially with their own families.

Under ordinary conditions a man loses about three-quarters of the heat he produces by radiation and conduction from the surface of his body. About one-quarter is lost by the evaporation of water from skin and lungs. Therefore the increased heat production in hyperthyroidism manifests itself in a warm skin which breaks out into sweat on slight provocation. The patient even while at rest feels warm, just as if he were exercising. He needs but little covering at night. To supply all this extra heat it is necessary for him to eat large quantities of food.

We have seen that in the cases here presented the basal metabolism has been an acurate guide as to the degree of thyroid activity. The question naturally arises as to whether or not this holds good for all cases. Past experience has shown that there are few pathognomonic signs in medicine. Particularly in diseases of the ductless glands scores of tests have been discarded as worthless. It will take several hundred metabolism experiments with patients carefully standardized from the clinical viewpoint before one can say that the basal metabolism is an absolutely accurate guide in the diagnosis and treatment of thyroid disease. We can, however, at the present time say that it is the best guide, much safer than any other one sign or symptom. It is a better guide in doubtful cases than the opinion of nine out of ten consultants.

The test has a firm physiologic and pathologic basis. It is purely objective, and cannot be influenced by the hopes of the patient or his physician. Since the phenomenon was first discovered by Friedreich Müller in 1893 and confirmed two years later by Magnus-Levy, its significance has not been disputed, although it has been grossly ignored. In Germany the level of the metabolism has been used in a few experiments as a method of testing different forms of treatment. In this country, shortly before the war, a large number of observations were being made in various clinics. In recent publications by Means and Aub,[1] White and Aub,[2] and by Peabody, Wearn, and Tompkins[3] it seems to be accepted as a standard of thyroid activity. Peabody has shown that a large proportion of the cases referred to the Army General Hospital at Lakewood as hyperthyroidism were incorrectly diagnosed.

Granting the value of the test, is it practicable? Calorimeters are out of the question except in a few laboratories. On the other hand, the simpler forms of apparatus for determining the basal metabolism are comparatively reasonable in cost and fairly easy to operate. They are much less expensive than an electrocardiogram and the technic is not so difficult. Still there are many pitfalls waiting for the careless investigator, and it is advisable that any man who starts to measure the total metabolism should begin with a series of normal controls.

"But why," says the practitioner, "should I, who have seen hundreds of cases, go to all this trouble when I can perfectly well tell from the clinical aspect whether or not the metabolism is increased?" Such guessing is very common, quite fascinating, and not risky for one's reputation unless the results are checked. On the other hand, those clinicians who have checked up their guesses in two or three hundred experiments realize the fre-

[1] Means, J. H., and Aub, J. C., A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, Jour. Amer. Med. Assoc., 1917, 69, 33.

[2] White, P. D., and Aub, J. C., The Electrocardiogram in Thyroid Disease, Arch. Int. Med., 1918, 22, 766.

[3] Peabody, F. W., Wearn, J. T., and Tompkins, Edna H., The Basal Metabolism in Cases of the "Irritable Heart of Soldiers," Medical Clinics of North America, September, 1918, U. S. Army Number.

quency of their errors, especially in atypical cases, and are not at all surprised if they do not come within 40 per cent. of the true figure.

The diagnostician who interprets the basal metabolism intelligently will be able to determine the degree of thyroid activity. The surgeon who operates on thyroid patients will find that the basal metabolism is of great help in following his results. He will also find that in many cases a fifteen-minute test with the respiration apparatus will save the patient a needless operation.

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ETIOLOGY AND TREATMENT OF BRONCHIAL ASTHMA.*

By William C. Thro, M. D.,
New York,
(From the Department of Clinical Pathology of the Cornell Medical College.)

Recent investigations have thrown some light on that obscure condition called bronchial asthma, with the profitable result that such investigations have led to the alleviation of the symptoms of this distressing disease in a number of patients. While speaking of therapy it is hardly necessary for me to add that before the patient is treated for bronchial asthma it must be ascertained that the symptoms are not due to cardiac, renal, pulmonary or pituitary disease. Due consideration must also be given to the idea advanced by Pottenger (1) as to the relation of the vagus to the disease. Recent investigations have added confirmatory evidence to the statement made by Meltzer (2) and Wolff-Eisner that asthma is to a great extent a manifestation of anaphylaxis or allergy. It was found, that in the lungs of animals that had died of anaphylactic shock, there was a contraction of the bronchioles (3) and it is supposed that a similar condition exists in the asthmatic spasm. The nerve centre controlling the muscles in the bronchioles in asthmatics is in a state of unstable equilibrium. These ideas are more acceptable than the idea that asthma is due to a congestion of the mucous membrane in the lungs.

It might be well to digress here to refresh our minds a little on this subject of anaphylaxis. The name was used by Richet before the investigations

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of Rosenau and Anderson or of Otto were made. The meaning of the word is the opposite of prophylaxis, that is hypersensitiveness or hypersusceptibility. Von Pirquet in his work on tuberculosis, in which he devised the skin test named after him, used the word allergy, which is another term for the same phenomenon. Dr. Theobald Smith had noticed this hypersusceptibility in guineapigs used in testing horse serum and as a result of his suggestion Otto performed his research on anaphylaxis, which appeared at the same time as the paper of Rosenau and Anderson. These investigations showed that it was the proteid substances that sensitized the animal.

Since von Pirquet's work, the skin reaction or modifications of it have been used in glanders, typhoid as the typhoidin reaction of Gay (4) the skin reaction to pneumotoxin (5) and recently in hay fever, asthma and as a test to detect food sensitization especially in children. The sudden cuticular reaction of Jenner, noted at the time of revaccination against smallpox, may also be mentioned. It is now generally believed the skin reaction is brought about as follows: The antibodies (which are formed in cells by the action of protein), if few in number, are all attached to the cells. On the introduction of the protein substance to which the animal is sensitive a reaction occurs in the sensitized cells, that is, in those cells to which the antibodies are attached. This in brief is the cellular theory that seems to have been proved by the researches of a number of investigators. Another explanation is that infection with the tubercle bacilli, for example, causes the production of antibodies which unite with the tubercle proteid when it is rubbed in the skin and a toxic substance is formed which causes the symptoms of anaphylaxis or allergy. The toxic substance is supposed to cause a dilatation of the blood vessels at the site of the scarification and it is in this way that the local reaction is caused.

Bronchial asthma is supposed to be in part the result of the sensitization of the patient to the proteids of bacteria, foods, and miscellaneous substances. For example, Walker states that in his series of patients studied fifty-five per cent. were sensitive to some protein and the nonsensitive were probably due to chronic bronchitis, cardiorenal complications, or emphysema. By some investigators it is thought to be a straight infection with bacteria. Hay fever, which is, as you know, closely related to asthma, is supposed to be due to sensitization to the pollen protein of certain members of the vegetable kingdom. This has been proved experimentally by Koessler (6). Urticaria (7), eczema (8), and angioneurotic edema are likewise supposed to be due in part to sensitization to various proteids.

In Walker's first bacteriological examination of the sputum of asthmatics he used plain agar and I have not yet seen any published papers showing his results with the blood agar. By using the latter he would be able to more easily detect Streptococcus viridans, Streptococcus hemolyticus, pneumococcus, and of course without any hemoglobin in the media which he used the influenza bacillus would be missed entirely. I may say here that Sicard (9) used blood agar and he found that the most universally present microorganism was Streptococcus viridans. Cecil (10) also found that the latter coccus was very prevalent in respiratory diseases. In fact it seems that it is one of the most common cocci of the respiratory flora.

However, Walker with the media he used found that Staphylococcus aureus and Staphylococcus albus were quite prevalent and he also isolated a diphtheroid on which he lays much stress as one of the possible factors in asthma. Bacterial proteids were obtained from a number of microorganisms and skin tests were made with them. He emphasizes the following: "During or immediately after an attack of asthma the skin reaction will be questionable." With his skin tests he obtained the

greatest number of skin reactions with Staphylococcus aureus, i. e., nineteen positive reactions out of ninety-seven tested, next with Staphylococcus albus and with Streptococcus hemolysans and a diphtheroid he obtained an occasional positive reaction. Out of forty-four patients tested with Streptococcus viridans he did not have a single positive reaction. I have heard several bacteriologists quoted as saying that the latter has no antigenic properties; but I do not know on what they base this assertion. I have looked up the literature somewhat on this subject and found that streptococci are capable of producing agglutinins, opsonins, and hemolysins. One investigator states that it can produce antibody, but that its power to do so is not marked.

In R. A. Cooke's (11) report on 100 selected cases of asthma he states that bronchial infection appears as the primary infection in only six per cent. of the cases. But in another part of the same paper he states that thirty-three per cent. of the patients had a complicating simple infection. Furthermore, as confirming the bacterial causation of some of the cases of asthma, Walker states that, "We have found that the serum of many patients that are sensitive to the protein of Staphylococcus aureus agglutinate strains of this organism." Treatment of the patients who were nonsensitive to this organism but whose serum agglutinated it, was followed by relief of the asthma. On the other hand, he obtained no positive agglutination tests when he used Staphylococcus albus. The results from skin reactions, complement fixations and precipitin reactions were more comparable with bacterial proteins. When Walker used the other proteins to which the patients were sensitive as antigens in complement fixation and precipitin reactions he found they were of no value in the diagnosis, prognosis, or treatment of the condition.

R. A. Cooke divides his patients into two groups, namely anaphylactic and nonanaphylactic.

Walker also divides his into two groups, using the term sensitive and nonsensitive. Out of 150 patients studied by the latter with the skin reaction fifty-five per cent. were sensitive to some protein. In Walker's series, the horse, mainly the dander, was responsible in twenty per cent. of the cases. In Cooke's forty-four per cent. reacted to animal dander. It must be remembered that while Cooke used the intradermal injection as his method of determining sensitization, Walker used the skin abrasion method. Cooke's is probably more sensitive. Next in importance as causative factors Walker places the proteins of wheat, Staphylococcus aureus and early pollens which were responsible for fifteen per cent. The late pollen Walker considered responsible for ten per cent., the cat in five per cent., Staphylococcus albus in three per cent. Of the miscellaneous proteins one patient was sensitive to casein, one to egg, two to chicken meat, one to feather, and one to flaxseed.

Of Cooke's cases thirty-three per cent. were sensitive to early pollen, thirty-one per cent. to late pollens, and thirty-four per cent. to food proteins. It is necessary to keep in mind the different methods used in applying the protein, Walker recognizing this when he states "that it is possible that the intradermal method would change some of the nonsensitive to the sensitive group." But Walker suggests that perhaps the intradermal method is too sensitive and it is not so easy to apply. Furthermore one of the investigators in our laboratory had such tremendous reactions that he became alarmed when he used the intradermal method. Bearing these facts in mind it is perhaps safer for the general practitioner to use the skin abrasion method.

Of the patients with asthma who seem to be sensitive to pollens the greatest number react to ragweed. They react next to goldenrod and next to timothy. It is better in the determination of seasonal asthma to test patients with the pollen of all the common plants rather than with one plant from each family.

In my own limited number of patients, thirty in number, tested with bacterial proteins, I found very few positive reactions, and besides they were not marked reactions. On the other hand Walker believes that the cutaneous test has proved to be of value in determining a bacterial cause in some of the patients. In the patients nonsensitive to the abrasion method it is possible that the intradermal test would demonstrate bacteria as the causative factors in some asthmatics. As I have mentioned previously, in the testing of patients to get an idea of sensitiveness to proteins it is advisable for practitioners to use the skin abrasion method, Walker believing, as I have stated before, that for general purposes the intradermal test is too sensitive.

In using the skin abrasion method thoroughly clean the flexor surface of the forearm with fifty-five per cent. alcohol and with a small pipette or a platinum loop place a drop of decinormal sodium hydroxide near the anticubital space and below and to one side place another drop. With a von Pirquet borer or a Hagedorn needle abrade the skin through the first drop and use this as a control. Do not bring the blood. To the second drop I add with a small platinum spatula a small amount of the dried proteid to be used and abrade the skin. Take care not to mix the proteids. If you use the platinum loop it can be burned after each trial. Some use a fresh tooth pick with each protein. Unless you plan to use every protein which you have it is advisable to question the patient as to sensitiveness to substances and thus the test may be expedited. A very positive reaction appears within a few minutes and consists of a wheal at least one centimetre across with a sharply demarcated, raised and jagged border and this wheal may be surrounded by an area of erythema. In some cases the reaction may be positive, although there is only an extensive erythema, but of course it must be much larger than the control. It is advisable to write down the list of proteins as you intend to use them before

performing the tests and then lay the small vials out on the table in the order as noted on the list. When good strong reactions are obtained they are truly remarkable and convincing and when, as often happens, the reactions agree with the statements made by the patients as to sensitiveness to certain foods or other proteins the results are truly gratifying.

In my personal investigations I have tested thirty-four patients with bronchial asthma, one with chronic bronchitis and three with hay fever. I have used thirty-two proteid substances and two pollens, ragweed and timothy. Of the thirty-two proteid substances four were bacterial, made by myself. They were made from Streptococcus viridans, Streptococcus hemolysans, Staphylococcus aureus, and a chromogenic gram negative coccus isolated from the sputum of an asthmatic patient. The bacterial proteids were made from microorganisms grown on agar, from which they were removed, washed with saline twice, and then washed with alcohol containing carbolic acid twice, and finally washed with ether and then allowed to dry.

Of the thirty-four patients who had asthma I tested thirty with the four bacterial proteids, of whom only three reacted to the chromogenic gram negative coccus, one reacted very slightly to Streptococcus hemolysans, and one reacted very slightly to Streptococcus viridans. Of the twenty-four tested with dog's hair two gave a marked reaction. Of the twenty-four tested with cat's hair one gave a very slight reaction. Of the twenty-six tested with horse dander one gave a very slight reaction. Twenty-three were tested with egg yolk and all were negative. Thirteen were tested with egg white of whom one gave a very marked reaction and one a very slight reaction. Of ten tested with cow's milk one gave a marked reaction. The patient who reacted very markedly to egg white and cow's milk

was a boy of nine years of age. About two weeks after the first reactions were obtained he was again tested with the same substances and gave identical reactions.

A few asthmatics were tested with the common cereals such as buckwheat, corn, rye, oat, barley, wheat, and rice, with indifferent results, since only a single marked reaction was obtained. A few of the patients were tested with the meats, such as beef, pork, lamb, and chicken. Out of these there was one moderate reaction. A very few were tested with fruit protein, and one marked reaction with banana was obtained. The patient, a young man, was asked before the tests were made as to the foods that seemed to cause him distress and since he mentioned the banana this was tried first and a marked reaction obtained. A very few were tested with the common shell fish and with one patient a moderate reaction to lobster was obtained. One young woman was tested with the thirty-four substances, including the two pollens. She reacted moderately to lobster protein and on being questioned it was ascertained that thirty-six hours previous to the test she had eaten lobster. The patient abstained from lobster but a few weeks after having the tests performed she ate some scallops and very soon thereafter she had an attack of asthma. She never reacted to clam or oyster proteins. The reaction was called marked if there was a large irregular wheal with erythema, it was called moderate if the wheal was smaller, slight if there was a large area of erythema only, and very slight if there was an area of erythema slightly larger than the control.

THERAPY.

Since it has been almost definitely established that asthma is due in over half the patients to a sensitization to protein it now remains to state how this information may be applied. The skin reaction may

in this respect enlarge its usefulness since the reaction is of great value in prognosis and in checking up the treatment.

An interesting application of these discoveries is stated in *Science* (12). It was ascertained by study that the California native black walnut was probably responsible for a considerable amount of hay fever in that State. The patients were tested by the intradermal method with extracts made from walnut pollen and a number of positive reactions were obtained. All the individuals used as controls were negative. A number of patients were relieved by leaving the regions where the walnuts abound during the season of pollenation. Many of the patients are being treated with the pollen extracts, but the results have not yet been announced.

Patients sensitive to proteins of horse dander, dog's hair, cat's hair, and pollens are relieved by a process of desensitization. It is unfortunate that the effects are transitory, especially with hay fever, and that consequently every year the patient has to go through a series of prophylactic inoculation before the appearance of the causative pollen. In desensitization the patient is given a set of injections with gradually increasing amounts of pollen protein. These amounts are accurately ascertained by R. A. Cooke and Vander Veer (13) by determining the amount of total nitrogen which the doses contain.

With patients sensitive to food proteins it seems that the only recourse is in abstinence from the foods which cause disagreeable reactions. That something, however, is possible in the way of desensitization to food products is apparent from the excellent work done by O. M. Schloss (14). His immunization was accomplished by the use of capsules given internally and containing not the whole substance, but one of the isolated proteids. His results were very satisfactory.

As to the vaccine therapy it seems to be the consensus of opinion of several investigators that some

of the patients are relieved by injections of vaccines. Walker (15) found that patients were relieved if they were injected with vaccines made from the microorganisms to which they were sensitive. This he found to be true with Staphylococcus aureus, Staphylococcus albus and diphtheroids. Also Walker found that certain nonsensitive patients, whose sera, however, agglutinated Staphylococcus aureus, were relieved by vaccines of the latter.

Sicard (9) also reports some successful results in the use of vaccines. Hutcheson and Budd (16) give a favorable report on vaccines in asthma. My opinion, based on the use of vaccines in a considerable number of patients, is that vaccine therapy in asthma is still in an experimental stage. I have seen patients who were considerably relieved by a few injections of vaccine but with these we must always keep in mind the mental effect of such a procedure. Then there are other patients who do not improve at all after a considerable number of injections. With these there is a possibility that we have not arrived at the true causative factor. More valuable data on vaccine therapy, however, will be obtained by carefully observed injections of sick patients than by experiments on a healthy animal of another species. I say this although fully cognizant of the basic principles of immunity that were discovered by the latter procedure. Although still in a vacillating state of mind as to the efficacy of vaccine therapy in asthma I believe that some useful knowledge has really been gained as to the etiology and treatment of bronchial asthma.

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THE STIMULATION AND INHIBITION OF THE GASTRIC SECRETION WHICH FOLLOWS THE SUBCUTANEOUS ADMINISTRATION OF CERTAIN ORGAN EXTRACTS

JOHN ROGERS, JESSIE M. RAHE and ELEEZA ABLAHADIAN

From the Johnston-Livingston Fund for Experimental Medicine, Cornell University Medical College

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In a previous communication (1) we showed that the subcutaneous injection in dogs of saline extracts of several different organs was followed in each case by an increase in the gastric secretion. Extracts made from the adrenal and pituitary glands alone, of those tested,. inhibited the gastric secretion both before and after the injection of the stimulant extracts.

These extracts were made by shaking for two hours the hashed fresh organ in normal salt solution which had been made slightly alkaline with NaOH. This was then stored in the ice box for twenty-four hours. After straining off the coarser particles through gauze and filtering through paper, enough 10 per cent acetic acid was added to the opalescent filtrate to precipitate the nucleo-proteins. After their removal the filtrate was boiled and again filtered to separate the acid albumins and this filtrate rendered faintly alkaline to litmus was, also boiled and filtered. This final slightly alkaline liquid then contained only the non-coagulable portion of the original saline extract and for convenience was designated as the "residue" of this or that organs The injection into dogs of the "residue" of each of the endocrine glands was followed by some definite and immediate physiological reaction which seemed traceable to either stimulation or inhibition of a part of the involuntary nervous system.

In the case of the thyroid, none of the coagulable materials in its saline extract were found capable of producing any demonstrable reactions.

For the adrenal, however, further experimentation has shown that almost as vigorous responses could be excited in the stomach by the adrenal nucleo-proteins as by the adrenal "residue." The latter is

rich in epinephrin while the nucleo-proteins contain only traces of this substance.

In the following article we have confined ourselves to the study of the effects upon the gastric secretion of the subcutaneous injection of extracts of the pituitary and adrenal glands and more particularly of the thyroid. We had previously employed dogs in which the usual Pawlow gastric pouch and fistula had been established, but as this operation seemed liable to damage the nerve supply of the pouch, we have employed in these experiments the Janeway fistula. A trap door flap about 2 inches square, with its base at the greater curvature, is cut from the anterior surface of the stomach. The flap is turned back and folded together by a continuous suture which unites the right and left borders of the flap and then the right and left edges of the gap in the stomach. The open extremity of the resultant artificial tube, which is continuous with the interior of the stomach, is then brought out through a stab wound in the left rectus and sutured to the skin. This fistula does not leak and after the wounds have healed, readily allows the passage of a catheter for obtaining the gastric secretion.

During the tests the animals have been placed in a retaining frame in which they can be kept quiet for an hour or more. Our dogs were given no food for at least twelve hours before the test. To make them react satisfactorily the animals must be maintained in the best possible condition.

Disease or malnutrition very evidently interferes with the amount of gastric secretion and with the responsiveness of the stomach to the test materials. The thyroid extracts were standardized according to both their iodine and nitrogen content, and the adrenal and pituitary extracts according to their nitrogen content alone. The injections were made with every aseptic precaution, usually into the subcutaneous tissue at the back of the neck. Then, with the dog standing in the retaining frame, a catheter was introduced into the fistula and the gastric secretion collected during successive fifteen-minute periods.

A great number of tests were made and table 1 shows a fair average of the results for the different preparations from the thyroid. It was found to be difficult or impossible to use the same dog for each test because a twenty-four-hour rest period, at the least, had to be allowed to maintain the animals in good condition. This often had to be much extended. The feeding took place in the afternoon, and the morning hours, when the stomach contains no food, were used for the experiments. In the second column of table 1 are noted the

(normal) quantity in cubic centimeters of gastric juice, collected during the first fifteen minutes and its total acidity expressed as HCl. This was determined by titration against $\frac{N}{10}$ NaOH, with phenolphthalein as the indicator. In the next column are noted the thyroid materials and the amount injected expressed in terms of its iodine and protein content. The next three columns represent the quantity and total acidity of the gastric juice collected during the three fifteen-minute intervals which follow the brief period required by the experimenter to make the test injection and then note the time. That is, about five minutes elapse between the close of the collection of the normal flow and the beginning of the collection of the test flow.

As remarked before, we had previously determined that the "residue" of a saline extract of the thyroid of any given animal, when standardized by its iodine content, was quite uniformly active. Of the common abattoir animals, the pig thyroid contains the largest amount of iodine, the sheep contains much less and the beef, the least iodine of the three. Incidentally it should be noted that sheep thyroids are very often goitrous and hence have an extremely low iodine content, and therefore care must be used to select only normal glands. Their iodine content, as is well known, shows a considerable seasonal variation, being the richest during the spring and summer months.

The first test in table 1 shows the comparative activity upon the stomach of the "residue" or non-coagulable portion of saline extracts of the pig, sheep and beef thyroids. The next tests show the comparative activity of pig thyroids, which were obtained from the abattoir in as *fresh* a condition as possible, and immediately extracted, and of those which had been kept before extraction, in a *frozen condition for about two weeks;* and finally, of the activity of an extract or "residue," made in exactly the same way as the others, from the commercial desiccated thyroid powder, which presumably consists of sheep thyroid glands.

As the active material in our "residues" is non-coagulable, we next tested alcoholic and ethereal extracts of the pig thyroid. The hashed glands were shaken for two hours in ether or 95 per cent alcohol, and stored for several days at room temperature, in corked bottles. The alcoholic or ether extract was filtered so that we obtained a clear liquid and then the alcohol or ether distilled off until only about one-eighth to one-tenth of the original volume remained. This was then diluted with distilled water and tested as to iodine and nitrogen content. A similarly prepared 95 per cent alcohol extract of commercial desic-

TABLE 1

Effects upon the flow of gastric juice and its acidity, which follow the injection of thyroid and other "extracts"

DOG NO.	NORMAL FLOW FIRST 15 MINUTES AMOUNT HCl		MATERIAL INJECTED	AMOUNT	EFFECT DURING SECOND 15 MINUTES AMOUNT HCl		THIRD 15 MINUTES AMOUNT HCl		FOURTH 15 MINUTES AMOUNT HCl	
	cc.	*per cent*			*cc.*	*per cent*	*cc.*	*per cent*	*cc.*	*per cent*
XX	3.0	0.46	Pig thyroid residue	7.0 cc. = {0.2 mgm. I 0.19 gram Prot.	21.5	0.52	21.0	0.54	10.0	0.54
XX	1.5	0.4	Sheep thyroid residue	10.0 cc. = {0.125 mgm. I 0.25 gram Prot.	6.5	0.52	6.0	0.48	5.0	0.48
XXII	3.4	0.36	Beef thyroid residue	2.8 cc. = {0.028 mgm. I 0.1 gram Prot.	4.0	0.44	3.0	0.4	2.0	0.4
XXIX	5.0	0.33	Pig thyroid residue "fresh" glands	4.0 cc. = {0.1 mgm. I 0.4 gram Prot.	13.0	0.33	10.0	0.45	9.0	0.44
XXIX	1.0	0.4	Pig thyroid residue frozen 2 weeks	4.0 cc. = {0.1 mgm. I 0.4 gram Prot.	12.0	0.5	13.0	0.5	8.0	0.45
VIII	3.4	0.36	Sheep (?) thyroid residue from commercial desiccated powder	2.5 cc. = {0.2 mgm. I 0.075 gram Prot.	7.0	0.36	6.0	0.38	4.0	0.34
XXIX	4.0	0.5	95 per cent alcohol extract pig thyroid	3.0 cc. = {0.033 mgm. I. 0.3 gram Prot.	15.0	0.65	16.0	0.6	14.0	0.6
XXIX	2.0	0.36	Ether extract pig thyroid	2.0 cc. = {Trace I 0.1 gram Prot.	4.0	0.43	5.5	0.46	4.0	0.46

XIV	4.0	0.28	95 per cent alcohol extract desiccated commercial (sheep) thyroid	2.8 cc. =	0.15 mgm. I 0.1 gram Prot.	8.0	0.36	7.0	0.3	7.0	0.3
III	2.6	0.3	Distilled water extract pig thyroid	5.0 cc. =	0.08 mgm. I 0.1 gram Prot.	1.0	0.36	1.0	0.36	Few	drops
VIII	2.6	0.3	Solution of Kendall's preparation from pig thyroids	2.1 cc. =	0.1 gram Prot.	1.5	0.28	1.5	0.28		
III	1.5	0.4	Beef muscle residue	4.0 cc. =	0.1 gram Prot.	1.5	0.4	1.0	0.4		
XXX	Few drops		Edkin's "gastrin"	7.0 cc. =	0.1 gram Prot.	8.0	0.5	11.0	0.58	5.0	0.5

cated thyroid powder (presumably from sheep glands) was also tested. An extract, according to Kendall's method (2) published in 1915, was made and tested. It had a high nitrogen and iodine content.

To show that a "residue" of any tissue is not active there is inserted a test made with the non-coagulable part of a saline extract of beef muscle. In the last line there is recorded for comparison a test made with Edkin's "gastrin" (3).

From the above figures it can be seen that a dose of the pig, sheep or beef thyroid which contains approximately the same amount of protein, varies considerably in the amount of iodine. And the greater the amount of iodine, the greater is the stimulant effect. The "residue" of the pig thyroid increases the gastric flow usually about sevenfold, of the sheep thyroid about fourfold, while the beef gland shows only slight activity. The total acidity is regularly increased but not to any such extent as is the quantity of gastric secretion.

There is a general belief that glands obtained in as "fresh" a condition as possible are preferable to, or more active than, those which have been stored for days or weeks, in a frozen state. In all our tests the frozen glands were fully as active as the "fresh." This is a matter of considerable importance as glands in quantity, for commercial purposes, practically must be stored for a greater or less length of time. The "residue" or alcohol extract of the common desiccated powder of sheep thyroid glands is only about half as active as corresponding preparations from fresh glands. Extracts of the dried material also show an increase in the protein content with a decrease in iodine, and this circumstance combined with its demonstrably lessened activity indicates some deterioration in quality.

An alcohol extract of the thyroid contains a little less iodine and more protein than our "residue" and is somewhat less active, and the average of a number of tests of comparable doses of the alcohol and saline or "residue" extracts shows that their stimulant powers upon the stomach are much in favor of the "residue." An ether extract consists almost entirely of fatty material which for injection has to be made into an emulsion with distilled water. This contains only traces of iodine but shows considerable activity. An ether-alcohol extract shows approximately the same activity as one made with alcohol alone.

The injection of a solution of Kendall's thyroid "active principle," as described above was followed by no response. An extract of pig thyroid made with distilled water was proved by repeated tests to be entirely inert. Thus evidently indicates that hydrolysis is necessary

before the active thyroid material can be obtained in watery solutions. Tests with a "residue" made from beef muscle prove only that hydrolyzed extracts of these organs have no stimulant effect upon the stomach, but the observation is inserted to show that "residues" of all tissues are not gastric activators.

The normal human thyroid contains approximately the same amount of iodine as the pig gland, or about 0.3 mgm. per gram of fresh tissue, and a "residue" or alcohol extract of this is closely comparable in its effects upon the stomach to a similar extract from the pig thyroid. The human organ in an individual who shows the symptoms of hyperthyroidism, is usually enlarged symmetrically, and is of even consistency throughout, in which case the infolding and proliferation of the alveolar epithelium characteristic of its supposed overactivity occurs more or less abundantly according to the severity of the symptoms, and in pronounced cases involves the entire diseased gland. Or it may be asymmetrically enlarged and of uneven consistency, in which case there are usually one or more encapsulated adenomatous or cystic or mixed cyst-adenomatous masses with the characteristic hyperthyroid changes surrounding, but not in the tumors. From these solid adenomata and from typical hyperthyroid glands, obtained fresh from operations, extracts were made as from the pig thyroids and the results recorded in table 2.

It will be noted that the first three tests are recorded from extracts from "human goiter." These were solid adenomata obtained from patients who presented moderate symptoms of hyperthyroidism, but the histology of the excised tissue showed only simple adenoma. The two last tests were each made with extracts of portions of glands containing the characteristic hyperthyroid changes and were obtained from patients suffering from typical exophthalmic goiter. Many other tests were made with extracts from similarly diseased thyroids, but like these, all were uniformly negative. Unfortunately there was seldom enough tissue to make both an iodine and a nitrogen determination, and as these experiments were carried out as material could be obtained, while tests with other organ extracts were in progress, only the protein content of the dose was ascertained. This permitted comparisons with organ extracts other than the thyroid, but there was never any response. That is, the symptoms of hyperthyroidism are apparently not *directly* due to an excessive quantity of thyroid product. Clinically the severity of the disease certainly does not seem to bear any relation to the size of the gland. Neoplastic epithelia are not

TABLE 2

Effects upon the flow of gastric juice and its acidity, which follow the injection of extracts from pathological human thyroids

DOG NO.	NORMAL FLOW FIRST 15 MINUTES AMOUNT HCl		MATERIAL INJECTED	AMOUNT	EFFECTS DURING SECOND 15 MINUTES AMOUNT HCl		THIRD 15 MINUTES AMOUNT HCl		FOURTH 15 MINUTES AMOUNT HCl	
	cc.	*per cent*			*cc.*	*per cent*	*cc.*	*per cent*	*cc.*	*per cent*
XV	3.0	0.21	'Residue' of simple human goiter	2 cc. = 0.19 gram Prot.	2.0	0.24	1.5	0.2	Few drops	
XVIII	8.0	0.27	'Residue' of simple human goiter	7 cc. = 0.1 gram Prot.	5.2	0.36	5.0	0.36	2	0.3
XIII	5.0	0.22	95 per cent alcohol extract simple human goiter	12 cc. = 0.1 gram Prot.	3.6	0.2	2.7	0.2		
XV	4.1	0.18	95 per cent alcohol extract hyperthyroid human gland	10 cc. = 0.4 gram Prot.	2.5	0.36	Few drops			
VIII	8.0	0.37	Residue of human hyperthyroid gland	7 cc. = 0.1 gram Prot.	5.2	0.36	5.0	0.36		

generally believed to produce any secretion and the above experimental findings with thyroid adenomata seem to confirm this belief.

The lack of response from extracts of thyroids which showed active hyperplasia at least indicates so great a change in the quality of the product as to prevent the fulfillment of its usual function.

We next tested the effects upon the stomach of the subcutaneous injection of atropin, nicotine, commercial adrenalin and extracts of the adrenal and pituitary glands. In previous experiments (1) as remarked before, we had ascertained that the adrenal and pituitary were the only organs which seemed capable of inhibiting the gastric secretion. Nicotine was accidentally noted to have this effect and although it is understood to act upon some intermediate nervous mechanism it was employed as a comparison with atropin, which paralyzes the terminal filaments of the vagus.

The records given above are a fair average of a large number of tests. It is well known that the secretory activity of the stomach is very largely controlled by the vagi, stimulation of which increases the flow, and by the sympathetic which inhibits. It can be noted that a moderate dose of atropin very quickly stops the gastric secretion, presumably by paralysis of the terminal filaments of the vagus. Nicotine was tested in both large and minute doses and seemed to exhibit inhibitory powers somewhat less than atropin; the inhibition was about in proportion to the size of the dose. Certainly no stimulation could be detected after the administration of even very minute amounts.

Epinephrin is generally accepted as acting through some stimulant effect upon the terminal filaments of the sympathetic, and thus should inhibit the gastric secretion. The typical test with a 1:1000 solution of adrenalin hydrochloride recorded in the third line of table 3, shows that a moderate dose cuts down the normal flow of gastric juice about one-half. A similar dose of a "residue" or an alcohol extract of the adrenal, which contains considerably more epinephrin, suggests that these materials, because of their epinephrin content, act in proportion to it by stimulation of the terminal filaments of the sympathetic. But the injection of a comparable quantity of the adrenal nucleo-proteins, which contain only faint traces of epinephrin is as active or more so than the adrenal "residue" or the alcohol extract or commercial adrenalin. Presumably its effects upon the secreting gastric epithelium is like adrenalin and exerted through the intermediation of the terminal sympathetic filaments. But if it is even more active than adrenalin this fact arouses a suspicion that the active principle of the adrenal

gland may contain something more than epinephrin. That is, epinephrin which undoubtedly exists in the adrenal, may be only the stable part of a larger and more labile molecule.

The final three tests with extracts, first of the whole pituitary gland and then with similar preparations from its anterior and posterior lobes, show only that the anterior lobe of this gland seems to exert some inhibitory influence upon the gastric secretion.

TABLE 3

Effects upon the flow of gastric juice and its acidity, which follow the injection of atropin, extracts of the adrenal and pituitary glands, and of nicotine

DOG NO.	NORMAL FLOW FIRST 15 MINUTES AMOUNT HCl		MATERIAL INJECTED	AMOUNT	FLOW DURING SECOND 15 MINUTES AMOUNT HCl		THIRD 15 MINUTES AMOUNT HCl	
	cc.	*per cent*			*cc.*	*per cent*	*cc.*	*per cent*
VIII	4.1	0.3	Atropin sulf	15 mgm.	0.5	0.4	Few	drops
VII	2.2	0.2	Nicotine	1 mgm.	Few	drops	Few	drops
IX	6.0	0.65	1:1000 solution adrenalin chloride	3 cc.	3.0	0.65	2.0	0.65
VIII	3.1	0.33	Adrenal "residue"	3.0 cc. = 0.1 gram Prot	0.2	0.35	Few	drops
XI	2.6	0.53	95 per cent alcohol extract adrenal	6.3 cc. = 0.076 gram Prot.	0.5	0.44	0.15	0.63
XI	4.0	0.28	Adrenal nucleoprotein	4.75 cc. = 0.076 gram Prot.	0.1	?	Few	drops
XI	2.4	0.38	Pituitary residue	1.26 cc. = 0.076 gram Prot	1.0	0.36	0.9	0.38
VI	2.6	0.19	Residue anterior lobe pituitary	2.75 cc = 0.076 gram Prot.	0.9	0.14	0.8	0.1
V	1.5	0.3	Residue post. lobe pituitary	3.4 cc. = 0.1 gram Prot.	1.8	0.35	1.4	0.37

In table 4 are recorded the average results of a large number of tests to show first the stimulant effect which follows the injection of the thyroid "residue," and the effect upon this stimulation which follows the injection of *a*, atropin to paralyze the vagus; *b*, of adrenalin to stimulate the antagonist of the vagus or the sympathetic; *c*, of the adrenal "residue" which contains much epinephrin and presumably acts like the 1:1000 solution of adrenalin; *d*, of the alcohol extract of

TABLE 4

Effects which follow the injection of atropin, extracts of the adrenal and pituitary glands, and nicotine, after the injection of thyroid material has stimulated the flow of gastric secretion

DOG NO.	NORMAL FLOW FIRST 15 MINUTES AMOUNT HCl		STIMULATION BY	AMOUNT INJECTED	FLOW DURING SECOND 15 MINUTES AMOUNT HCl		INHIBITION BY	AMOUNT	FLOW DURING THIRD 15 MINUTES AMOUNT HCl		FOURTH 15 MINUTES AMOUNT HCl		LINE NO.
	cc.	*per cent*			*cc.*	*per cent*			*cc.*	*per cent*	*cc.*	*per cent*	
VIII	4.0	0.25	Thyroid residue	5.2 cc.=0.1 gram Prot.	17.0	0.38	Atropin sulf.	15 mgm.	6.0	0.38	2.2	0.3	1
XVIII	2.0	0.18	Thyroid residue	4.0 cc.=0.1 gram Prot.	16.0	0.27	Atropin sulf.	15 mgm.	9.4	0.42	9.0	0.48	2
XVII	1.5	0.12	Thyroid residue	4.0 cc.=0.1 gram Prot.	8.0	0.2	1:1000 solution adrenalin chloride	1.5 cc.	5.0	0.3	1.0	0.36	3
III	1.0	0.36	Thyroid residue	3.7 cc.=0.1 gram Prot.	12.0	0.55	Adrenal residue	3.0 cc.=0.1 gram Prot.	1.1	0.53	4.8	0.53	4
I	1.4	0.36	Thyroid residue	3.7 cc.=0.1 gram Prot.	7.5	0.47	Adrenal nucleoproteins	6.2 cc.=0.1 gram Prot.	1.2	0.42	0.15	0.32	5
III	0.2	0.2	Thyroid residue	3.7 cc.=0.1 gram Prot.	4.6	0.25	95 per cent alcohol extract adrenal	8.3 cc.=0.1 gram Prot.	1.6	0.21	1.8	0.27	6
VII	0.2	0.2	95 per cent alcohol extract thyroid	2.0 cc =0.1 gram Prot	7.4	0.24	Pituitary residue	2.0 cc.=0.1 gram Prot	4.0	0.21	3.0	0.27	7
VIII	4.8	0.28	Thyroid residue	4.0 cc.=0.1 gram Prot.	16.2	0.38	Nicotine	0.75 gram	11.0	0.36	7.5	0.38	8

the adrenal which is closely similar to the adrenal "residue;" *e*, of a solution of the adrenal nucleo-proteins which contains only traces of epinephrin; *f*, of the pituitary "residue," and finally *g*, of nicotine.

After stimulation of the gastric flow by the injection of the non-coagulable or "residue" part of a thyroid extract, paralysis of the vagus by atropin only checks the secretion. Atropin does not then completely stop the flow as it does in the unstimulated stomach. Adrenalin, on the other hand, which "activates" the sympathetic or inhibitory nerve supply of the stomach, only checks the *unstimulated* flow, and shows about the same amount of inhibition upon the stimulated secretion. The injection of the adrenal "residue" or of an alcohol extract of the adrenal, which are both rich in epinephrin, is followed by about the same decrease in the flow of the unstimulated, but a considerably greater decrease in the stimulated gastric secretion.

The injection of a solution of the adrenal nucleo-proteins which contains only traces of epinephrin, is followed by a similar and even a slightly more vigorous inhibition. These facts seem to indicate that the gastric nerves are very important, if not essential, for the stimulation produced by the thyroid and for the inhibition by the adrenal. Apparently also the thyroid acts through or upon the vagus and not, as is generally believed, upon the sympathetic. The inhibitory powers of the latter nerves are apparently intensified by some substance produced by the adrenal gland, in which epinephrin forms a part. This substance is probably not epinephrin alone, because adrenalin does not act as vigorously as do extracts of the whole adrenal gland, or the adrenal nucleo-proteins, in which, as stated previously, there are only traces of epinephrin (table 4, lines 3, 4 and 5).

The non-coagulable or "residue" part of a saline extract of the pituitary is the only other organ derivative which we have found to possess inhibitory powers over the flow of gastric secretion. It is interesting to note that extracts of the posterior lobe seem inert. The anterior only is active, but an extract of the whole gland proved more active than one of the anterior lobe alone. Nicotine is supposed to paralyze not the terminal filaments of the sympathetic, but an intermediate portion of the system. It was employed in these tests because it was unexpectedly found to inhibit the gastric secretion in more or less direct proportion to the size of the dose.

As yet we can offer no very definite explanation for these phenomena. Atropin quite evidently paralyzes and so stops the functionation of the "activating" or autonomic portion of the involuntary nervous system.

It is also evident that the adrenal product has a selective affinity for the terminal filaments of the sympathetic, as distinguished from the autonomic or vagus group of nerves. The thyroid product, on the other hand, seems to possess at least some of the same kind of affinity or stimulant power for the opposing or vagus group of filaments. It certainly does not stimulate the sympathetic, or its effect upon the stomach would be intensified and not decreased by the injection of either atropin or adrenalin.

Ergotin is supposed to paralyze the terminal filaments of the sympathetic, but in our experiments upon the stomach it was found to be so variable and uncertain as to be useless. Our extracts of the whole adrenal gland all contain at least traces of epinephrin, and therefore presumably act like it, i.e., through or upon the sympathetic. This, of course, brings into question epinephrin. Is it the normal active principle of the gland or only the stabile portion of a larger and more labile product? That cannot be answered from these experiments, although it is quite evident that extracts of the whole gland show a greater inhibitory effect upon the gastric secretion than does adrenalin.

DISCUSSION

The thyroid gland evidently stimulates, and the adrenal inhibits, gastric secretion. These effects are apparently produced chiefly through the intermediation of the vagus and sympathetic nerve terminals. The secretory functions of the vagus are apparently excited by some material which can be extracted from the thyroid by alcohol or by a process which involves more or less hydrolysis of the gland. The inhibitory powers possessed by the sympathetic terminals seem to be excited by all the extracts from the adrenal gland which were tested. Extracts from the entire gland are much more active than adrenalin. Can this activation or inhibition of the secretory cells of the stomach through their nerve supply in conjunction with thyroid and adrenal products be a process which is essentially one of nutrition? A prolonged stimulation like that produced by the thyroid extracts, when compared with the increased general metabolism which follows thyroid feeding, suggests that the thyroid product, with the intermediation of the vagus or secretory nerve impulse, increases the metabolism of the gastric epithelium. This means that it facilitates the absorption of nutritional material or "food" by the cells and the metamorphosis of this "food" into the cell's secretion. The adrenal product, on the other

hand, in conjunction with the sympathetic or inhibitory nerve impulse, can be imagined as preventing this metamorphosis. The nature of the impulses conveyed to the stomach by its double nerve supply is, of course, unknown but, as determined by electrical stimulation, the vagus evidently activates and the sympathetic inhibits this organ If the thyroid product has an affinity for the vagus terminals and promotes cell metabolism, and the adrenal an affinity for the sympathetic and retards this metabolism, then it is unnecessary to imagine two radically different kinds of nerve impulses. The chemical properties of the nerve endings are alone to be considered. The nature of the impulse in the vagus and the sympathetic can be the same, but the effects of its discharge from one nerve terminal or the other are regulated by the presence and amount of thyroid or adrenal, and probably many other products.

CONCLUSIONS

1. A slightly alkaline saline solution, or alcohol, extracts from the thyroid some non-coagulable material which is a vigorous stimulant for the gastric secretion.

2. This material produces its effects at least in part by intensification of the functions performed by the terminal filaments of the (gastric) vagus.

3. Extracts similarly made from the pathological tissue of adenomatous or hyperthyroid human glands are inert.

4. Extracts of the adrenal gland vigorously inhibit gastric secretion.

5. These extracts of the adrenal gland all contain more or less epinephrin and therefore it is presumable that their effect is produced by intensification of the inhibitory function which is ascribed to the (gastric) sympathetic.

6. Adrenalin is not as active a gastric inhibitor as the adrenal nucleoproteins obtained from extracts of the whole gland. These adrenal nucleo-proteins contain only traces of epinephrin.

7. Extracts of the pituitary gland also inhibit gastric secretion, but only about one-half as vigorously as do extracts of the adrenal.

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A CLASSICAL CASE OF HEMOPHILIC ARTHRITIS*

MAY G. WILSON, M.D.
Clinical Instructor Diseases of Children, Cornell University Medical College
NEW YORK

CASE—William B., 9½ years of age, born in Jersey City, N. J., of Italian parentage, has been under observation at the Cornell Children's Clinic for the past two years.

Family History.—His paternal history, as far as known, is free from hemophilia. On his mother's side the disease can be traced back two generations. His maternal grandmother died of tuberculosis. Whether she had any symptoms of hemophilia is doubtful. She had twelve children, several of whom died of tuberculosis. A history was obtained of only six of these children, two sons and four daughters. One of the boys died of tuberculosis. He was not considered a bleeder. The other died of hemorrhage when 18 years of age. He was a bleeder. One of the girls gave a history of purpuric spots, spontaneous ecchymosis and bruises following trauma from childhood. Of her offspring, two children, a boy and a girl, are not considered bleeders. The second girl had three children, boys, two of whom are bleeders. The third girl had eight boys, seven of whom are bleeders. One boy is normal. The fourth girl, the patient's mother, gives a similar personal history. She had twelve children and several induced miscarriages. Of eight boys and four girls, four boys and three girls are living. One boy died at 2 years of age following a convulsion. He was a bleeder. The other children died in infancy and were not considered bleeders.

The patient's sisters, aged 20, 16 and 7 years, respectively, all give a history of purpuric spots and bruises; no other symptoms. Two of his brothers, 13 and 17 years of age, respectively, give no evidence of hemophilia. The third brother, 24 years of age, gives a typical history. At birth a purpuric spot was noted on his face. He had frequent hemorrhages, spontaneous and following trauma. They were noted early. He had hematuria and epistaxis when 5 years of age; then followed the joint involvement at the age of 8. Frequent severe repeated attacks, involving the knee, ankle and elbow joints, left him a cripple, confined to bed almost constantly, until puberty, when the interval between attacks of hemarthrosis increased and the severity of the symptoms gradually diminished. For the past three years he has been free from joint involvement, but he has had some joint pains and ecchymosis. He still has some deformity and some stiffness of left knee, ankle and elbow (Figs. 5 and 6). It is interesting to note that he was accepted for limited military service, and in spite of a week of trench digging and hiking he did not have any return of symptoms. The patient is the fourth of these boys.

Summary.—In summing up the family history the following points are of special interest.

(1) The definite maternal transmission of hemophilia to the majority of the males through two generations. (2) The persistent evident hereditary purpuric tendency in the females. (3) The presence of typical hemophilia with arthritis in the brother, with recrudescence of symptoms after puberty. (4) The characteristic marked fertility and larger proportion of males in the offspring. (5) The history of tuberculosis.

General Physical Examination.—The patient is malnourished, anemic, dark complexioned with dark hair and eyes, of slender build, good intelligence and

*From the Children's Dispensary, Cornell University Medical College.

Fig. 1.—There is marked swelling of the left knee joint, slight swelling of the right elbow and thickening of the second phalangeal joint of the index finger of the right hand.

Fig. 2.—Lateral view of left knee joint. Note the characteristic posture.

Fig. 3.—Anteroposterior and lateral views of the left elbow, showing considerable enlargement of the centers of ossification for the head of the radius and external condyle. The center for the olecranon has not only appeared but has united. In the print of the right elbow this center has not appeared. It is seen normally at about the eighth year and unites with the shaft about the sixteenth year.

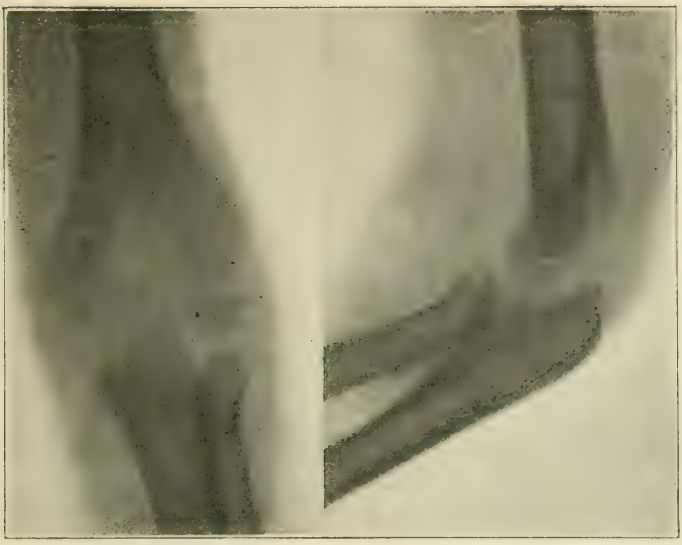


Fig. 4.—Anteroposterior and lateral views of the right elbow joint, apparently normal now; at least there is no marked roentgen-ray evidence that this joint is or has been involved.

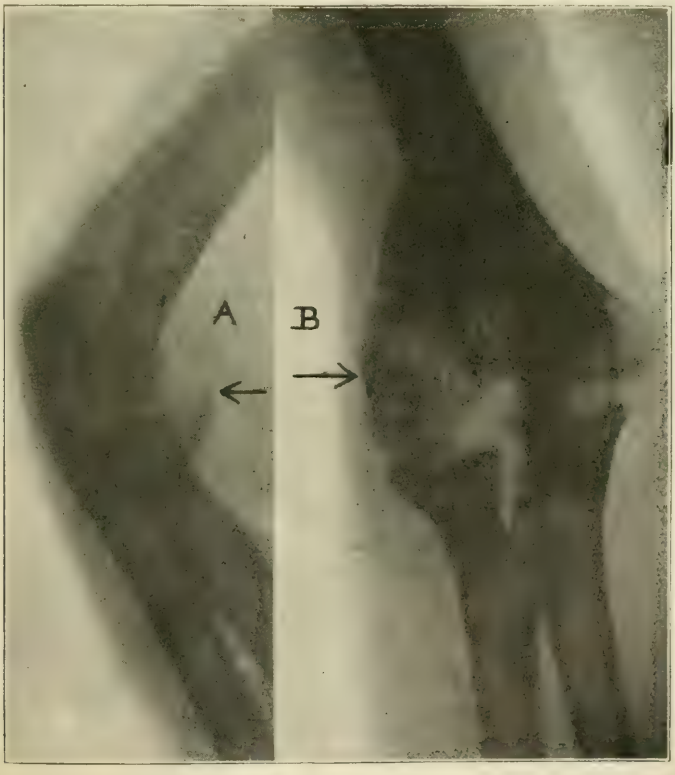


Fig. 5.—(a) Lateral view of left elbow of John B. (brother), 24 years of age, showing marked hypertrophy or enlargement due to an increase in lime salt deposit in the coronoid process of the ulna. (b) The anteroposterior view shows a similar condition present in the external condyle.

sanguine temperament, corresponding to the erethetic type of Wachmuth.[1] The throat, teeth, heart and lungs are normal. D'Espine's sign is present to the fourth dorsal vertebra. The liver and spleen are normal.

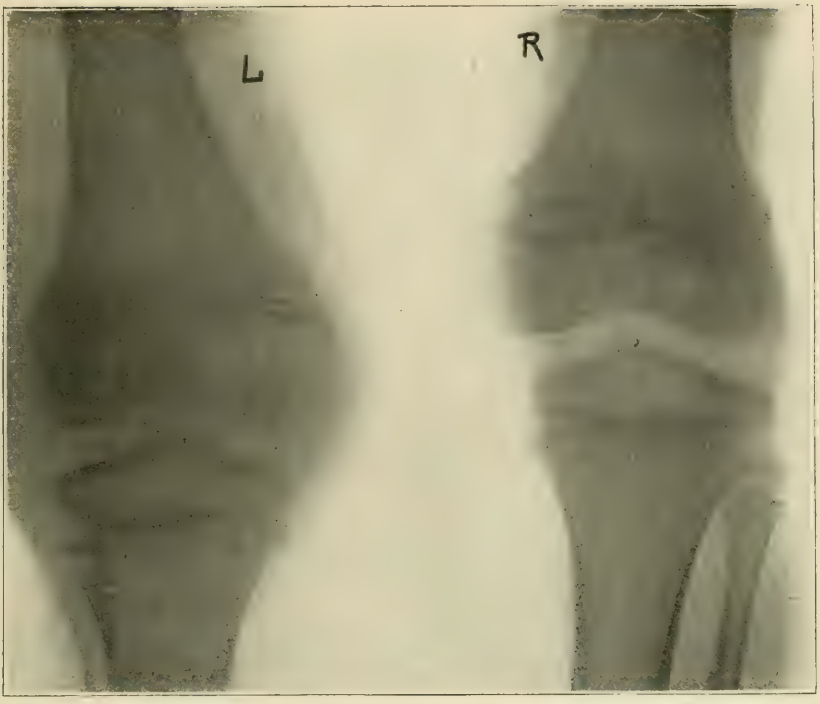
Personal History.—Although a normal birth, the boy was breast fed for two months. He had measles, scarlet fever and pertussis without any untoward symptoms or complications. He is subject to repeated attacks of bronchitis. Vaccination was not attended with any bleeding.

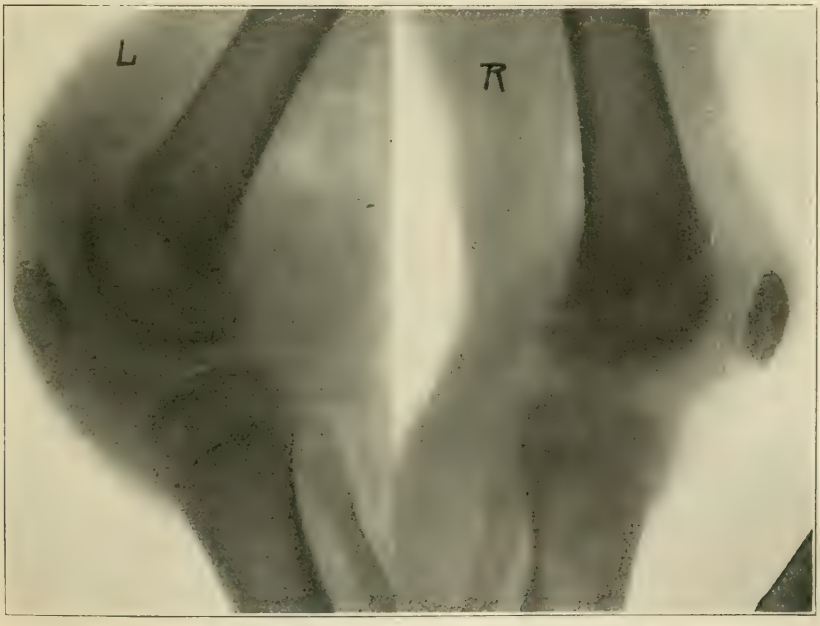
Hemophiliac History.—After birth a purple spot, the size of a quarter, was found on the palm of the right hand. This spot disappeared in a short time. (The mother claims that every male bleeder in the family showed some such spot at birth.) There was persistent oozing, not of great amount, from the umbilicus for one month. At 2 years of age the spots or spontaneous hem-

Fig. 6.—(a) The anteroposterior and lateral views of the left knee joint of John B. (brother) reveal the presence of spurlike projections and enlargement or elongation of the patella. (b) The anteroposterior view resembles a chronic hypertrophic osteoarthritic joint. It looks like an old man's knee joint.

orrhages under the skin and from the mucous membranes appeared. Slight trauma was followed by bleeding and bruises. When he was 3 years of age epistaxis almost proved fatal. First dentition was normal; second dentition was associated with constant oozing around the gums for several months. There is no history of hematuria. At 4 years of age he had repeated convulsions for two weeks, with a hemiplegia which cleared up. This is suggestive of a cortical hemorrhage. Recently a scratch of the tongue with a crust of bread caused bleeding that was controlled with difficulty. Ten days ago a

1. Legg, Wickham: Treatise on Hemophilia, London, 1872, p. 46.





Figs. 7 and 8.—Evidence of fluid is observed. The joint is hazy; the epiphyses present a hazy, irregular outline. Anteroposterior and lateral views of both knee joints show some enlargement of the epiphyses and the patella, the right being smaller. The lateral views show best the fibrous deposit along the joint side of the epiphyses of the femora. The process is a productive one, there being no evidence of destruction of either cartilage or bone.

hematoma, the size of a grape fruit, appeared in the left groin. It is now absorbed.

The first joint involved was the ankle. The patient was 5 years of age at the time. This attack was followed by repeated attacks involving the elbow and knee joint. Occasionally the smaller joints were affected at irregular intervals without any particular relation to climate or weather. There seems to be a definite history of trauma with many of the attacks. The usual course and symptoms of the hemarthrosis is as follows: Either following a trauma or spontaneous and preceded by prodromal symptoms such as acute pains in limbs and joints, facial pallor and anorexia for a few days, one or more joints suddenly become swollen and filled with fluid. They were hot, tender, not red, stiff and extremely painful. Associated with the local symptoms was fever varying between 102 and 103 F. and extreme prostration. After a week or ten days the local and constitutional symptoms abate, the effusion in the joints either is absorbed entirely, leaving a normal joint (as in the right elbow, which ten days ago was swollen to three times its size and is now normal except for a black and blue spot above the internal condyle, and a slight swelling), or as the result of repeated attacks there is left some stiffness as in the left elbow; or it remains the seat of a subacute or chronic process with distinct deformity and crippling, as in the left knee. This joint has been for the past three months (and is at present) swollen, painful and filled with fluid. No doubt the constant trauma in walking due to the deformity keeps up the effusion (Figs. 7 and 8).

Summing up there are noted, first, the bleeding, spontaneous and traumatic; second, the ecchymosis, petechiae and hematoma, both traumatic and spontaneous; third, the typical joint involvement as described by Franz Hoenig and illustrative of the pathology (Fig. 5).[2] (1) Hemarthrosis, effusion of blood in the joint; (2) subsequent attacks producing panarthritis and (3) end-result deformity and ankylosis (Figs. 6 and 7).

Blood Examination.—A careful blood study was made by A. F. Hess[3] two years ago and showed the following:

Date	Coagulation Time Plasma, Minutes	Coagulation Time Blood, Minutes	Remarks
11/13/14	52	90	
11/20/14	20	55	
11/24/14	...	106	
12/16/14	100	210	(Five days ago severe
1/14/15	24		bleeding from tongue)

Plasma of brother, M. B., 9 years of age, clotted in nine minutes. Plasma of brother, John B., clotted in twenty-six minutes. A recent test made at the base hospital showed clotting in fifteen minutes. Besides the marked delay in coagulation time there was diminished prothrombin content. The platelets were normal, from 200,000 to 300,000. The capillary resistance test was negative; puncture test was negative. The antithrombin test was normal. Adding calcium did not change the coagulation time.

Roentgen-ray examination showed the process to be one of production of fibrous tissue in the joints subject to repeated attacks, as can be seen in the illustrations. The hemarthrosis may clear up and leave a normal joint as is shown by the roentgenogram of the right elbow.

I am indebted to Dr. R. E. Herendeen from the department of roentgenology, Cornell University Medical College, for the excellent roentgenograms, and to Mr. William Dunn from the photographic laboratory of the college for the prints and photographs.

2. Bulloch and Fildes: Hemophilia, Eugenic Lab. Memoirs, Univ. of London, 1911, 12.

3. Hess, Alfred F.: The Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med. **17**:203 (Feb.) 1916.

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REPORT OF THE CORNELL NUTRITION CLASS

By May G. Wilson, M.D.

Clinical Instructor, Diseases of Children, Cornell University Medical College, New York.

It has been the custom at the Cornell Children's Clinic to inquire into the dietetic habits and hygiene of the so-called "delicate child" whenever this type of child presents itself to us for advice in the general run of patients in the childrens' clinic.

Because of the increasing number of these cases—children who keep so thin, do not eat anything, etc.—and the marked improvement following the special instruction given for the correction of the most prominent errors, it seemed advisable to try and improve our previous results by a more careful study of this group of children and to endeavor to discover and correct the causative factors. To this end the group or class method, so successfully worked out with "cardiacs," was planned.

Through the coöperation of Mr. Frank Manny of the Bureau of School Welfare, New York Association for Improving the Condition of the Poor, the Cornell Nutrition Class was organized May 1, 1917, and the following report is based on the work of this class from May to October, 1917, inclusive.

Schedule.—Monday and Wednesday 2—4 p. m.

Staff.

Physician—Owing to the scarcity of clinic assistants, one physician had entire charge of class.

Nurse—We were fortunate in having a nurse who had many years' experience in private homes with this type of case. She took charge of all home instruction and assisted in the clinic.

Social worker—Through the A. I. C. P. we had part time services of a social worker who assisted in referring cases to the clinic.

Two volunteer assistants for clerical work.

Routine of the Nutrition Class.

Initial Visit.—Each child was given physical examination; weight and height were taken. All necessary laboratory aids were used to assist diagnosis. Physical defects were noted; past and present complaints, dietetic habits and hygiene were carefully recorded on uniform blanks furnished by the A. I. C. P.

Instruction.—The importance of the correction of all defects having a bearing on the nutrition of the child was explained and the child was referred to the various departments of the Cornell Clinic for treatment. All errors of diet, hygiene and management were pointed out to the mother and her child and the urgency of immediate correction and supervision advised. Suitable *individual* diet prescriptions, with outline of future management, was given each child. The case was then turned over to the nurse who supplemented the physician's orders by more detailed instruction, giving cooking directions for diet ordered. An appointment was made for an early home visit. Children unaccompanied by mothers were given precedence in follow-up visits. The diet prescription consists of a printed slip having list of various articles of food and general directions. The food to be eaten was checked, frequency and portion inserted, suitable to the income and the requirements of each individual case. This method lays emphasis on the importance of the diet, and is better followed than the general diet list commonly used.

Home Visits.—This is the most important phase of the work. Here conditions and the problems of every day are encountered. The nurse consults with the mother and together they work out the problem of future management. To secure the coöperation of mother and child is essential for permanent results. Here the experienced and ingenious nurse is taxed to the utmost. The first visit is at least for one hour, subsequent visits may be a little shorter.

Boys' and Girls' Play Clubs.—Children living in the same neighborhood were organized into clubs, the child making the best progress or the natural leaders, being made captains. On warm days, the nurse would arrange through the captain to have the children meet at neighboring parks or playgrounds, giving us an opportunity of supervising the play to prevent fatigue, the latter being a great source of unnecessary loss of energy. The nurse would plan the play of the week, arrange for dental treatment and visits to the municipal bath. We found it of great advantage to keep our children together and away from the influence of their former playmates. Vacations in the country were arranged through the courtesy of Miss Givin of the A. I. C. P.; but these were too short to be of any value. We had no facilities or funds for giving relief and found no urgency for same.

Return Visits.—At first children reported each week, later, every two weeks, as the child's condition improved. Regular visits to the class and the strict following of orders were insisted upon, until the novelty of the régime wore off. At these visits, group or class instruction was used to advantage. Interest was stimulated by encouraging competition and awarding prizes for the greatest progress.

Source of Material.—Undernourished children were referred to us from the lists of the neighboring public school nurse, through the social worker of the A. I. C. P., and from our own clientele. The larger number came from the poorest sections of the city.

Total number of cases admitted 250. Cases making 1 or 2 visits 105 (not included in report). Total number of clinic visits 924 (boys, 439; girls, 485). Length of time under observation, 1 to 6 months; average, 3 months.

These observations were made during the vacation period, as this time offers an opportunity for better home and clinic control with the advantage of more out of doors and non-interference by the requirements of school attendance.

Nationality.

American	54
Italian	40
Russian	26
Irish	15
German	10
Total	145

Ages and Sex.

Ages	Boys	Girls
1 to 6 yrs.	10	16
6 " 10 "	22	32
10 " 12 "	15	12
12 " 14 "	14	11
14 " 16 "	10	3
Total	71	74

Grouping of Cases.—Some of the important physical characteristics of this group of children are as follows:

Under weight for age or height; under height; poor superficial circulation, as shown by lack of color of skin and mucous membranes, flabby skin and lack of muscular development; listless and of low vitality.

TABLE I.—DUNFERMLINE CLASSIFICATION.

Girls— Ages	1-6 yrs.	6-10 yrs.	10-12 yrs.	12-14 yrs.	14-16 yrs.	Total %
Nutrition 1	0	0	0	0	0	0
" 2	1	1	0	0	0	2 or 2.7%
" 3	5	8	5	5	0	23 or 31.0%
" 4	10	23	7	6	3	49 or 66.2%
Total.....	16	32	12	11	3	74
Boys—						
Nutrition 1	0	0	0	0	0	0
" 2	0	1	0	0	1	2 or 2.8%
" 3	6	5	2	1	2	16 or 22.6%
" 4	4	16	13	13	7	53 or 74.5%
Total.....	10	22	15	14	10	71

TABLE II.—WEIGHT-HEIGHT-AGE CLASSIFICATION.

NOTE.—Arbitrary limits of 10% above and below the normal standard for weight and 5% above and below the normal standard for height were used for *even weight* and *height*, while weights and heights above or below these limits were considered as *over* or *under*. Holt-Burk-Boas Standards used.

Girls— Ages	1-6 yrs.	6-10 yrs.	10-12 yrs.	12-14 yrs.	14-16 yrs.	Total %
Weight-Age Basis:						
Over Weight	1	1	1	1	0	4 or 5.4%
Under Weight ...	7	16	6	7	2	38 or 51.2%
Even Weight	8	15	5	3	1	32 or 43.2%
Weight-Height Basis:						
Over Weight	6	1	1	2	0	10 or 13.5%
Under Weight ...	7	21	5	7	2	42 or 56.7%
Even Weight	3	10	6	2	1	22 or 29.8%
Height-Age Basis:						
Over Height	3	4	2	3	0	12 or 16.2%
Under Height	7	9	0	3	2	21 or 28.3%
Even Height	6	19	10	5	1	41 or 55.3%
Boys—						
Weight-Age Basis:						
Over Weight	4	3	1	1	0	9 or 12.6%
Under Weight ...	5	10	7	12	9	43 or 60.1%
Even Weight	1	9	7	1	1	19 or 26.7%
Weight-Height Basis:						
Over Weight	2	6	1	3	1	13 or 18.3%
Under Weight ...	6	11	6	2	6	31 or 43.7%
Even Weight	2	5	8	9	3	27 or 38.0%
Height-Age Basis:						
Over Height	2	8	2	3	7	22 or 30.9%
Under Height	6	1	2	2	0	11 or 15.4%
Even Height	2	13	11	9	3	38 or 53.5%

TABLE III.—COMPARISON OF TABLES I AND II.

Dunfermline Scale—	Boys.	Girls.
Nutrition 3	22.1%	31.0%
" 4	74.5%	66.2%
Under Weight for Age.....	60.1%	51.2%
Under Weight for Height.....	43.7%	56.7%
Under Height	31.0%	28.3%

Tables I, II, and III give a classification of the 145 cases reported on, according to the three common methods: The Dunfermline scale; the relationship of weight to height and weight to age. The Dunfermline scale takes into consideration the above characteristics and classifies in four grades of nutrition; 1. superior; 2. passable; 3. poor; 4. very bad. This scale is of value as a quick method of classifying large numbers of children.

In examining children they should be stripped, weighed and measured. Superficial inspection passes the child with the round face and undernourished body. For adequate diagnosis the weight-height-age relationships should be utilized. (See tables III. and IV.

TABLE IV.—DISTRIBUTION OF DUNFERMLINE SCALE GROUPS ACCORDING TO

	Boys—Total 71.			Girls—Total 74.		
Weight-Age Basis:	N.(2)	N.(3)	N.(4)	N.(2)	N.(3)	N.(4)
Over Weight	1	5	3	1	1	2
Under Weight	1	7	35	0	11	27
Even Weight	0	4	15	1	11	20
Weight-Height Basis:						
Over Weight	0	5	8	0	5	5
Under Weight	0	8	23	1	11	30
Even Weight	2	3	22	1	7	14
Height-Age Basis:						
Over Height	1	7	14	2	5	5
Under Height	0	3	8	0	5	16
Even Height	1	6	31	0	13	28

The following summary of physical defects found in this group of children are the results of continued undernourishment, as well as contributing causes:—

Defective vision 6.2%
Defective hearing 6%
Hypertrophied tonsils (requiring removal) 5.5%
Hypertrophied tonsils (requiring observation) ..... 13. %
Adenoids 2.7%
Pulmonary—bronchial glands (tuberculous)..... 2. %
Cardiac—functional 8.9%
Cardiac—organic 6.8%
Nervous—chorea ..... 2. %
Orthopedic—flat feet, round shoulders (posture) ..... 26. %
Defective teeth—(in need of immediate care)..... 54. %

Of the previous contagious diseases reported to have preceeded the present condition: Measles—35% of cases; pertussis—20%; scarlet fever, 10% and diphtheria, 4%. The poor resist-

ance of the malnourished child to these diseases and their sequelae, are well known.

Other Previous Illness and Complaints.—The following group of symptoms are increasingly common complaints of this type of child:—

Constipation	48%
Recurrent vomiting	31%
Recurrent bronchitis	23%
Asthmatic bronchitis	15%
Rheumatism (as manifested in children by tonsilitis, growing pains, anemia, etc.)	21%

Dietetic Habits.—Some of the gross errors of diet and habit were as follows:— 71% indulged in sweets to excess; 23% drank tea and coffee; 23% drank beer. Eating too fast; irregular meals; food between meals; improper or badly cooked and insufficient food and lack of sleep were also common causative factors.

It is well known that children have a predilection for highly flavored food. This is partly due to the fact that such food acts as a stimulus to their disordered appetites and pampered palates, and partly because they have been habitually fed in accordance with the tastes of their elders.

The common dislike for plain, building foods such as cereal, vegetables and milk, due to the above diet and habits, is a serious problem. From the time the child gets its first taste of table food it demands and gets everything in sight. These errors of diet and habits, while due in a great part to ignorance of food values, is in the main due to lack of home training. After the mother has been educated as to preparation and purchase of food, then there is still the problem, *will the children eat?* To get the coöperation of the child has been found a most difficult task, but not an impossible one.

Poverty, while a factor in the nutrition problem, is not so great a one as we have been accustomed to think. It is not altogether lack of money, but money spent unwisely, without adequate return of food value, that results in underfeeding. Our work was only educational and we gave no financial assistance, yet of the 145 cases, 128 or 88% gained weight, and 105 or 74% showed 2.21 times the expected gain for the period under observation. Tables V and VI give the results in detail.

TABLE V.—RESULTS IN DETAIL.

Number making gain in Weight.	Number who remained same Weight.	Number who lost Weight.
Boys..... 65	Boys..... 4	Boys..... 2
Girls..... 63	Girls..... 5	Girls..... 6
Total..... 128 or 88 %	Total..... 9 or 6.2%	Total..... 8 or 5%

Number who gained more than expected gain.	Number who gained average expected gain.	Number who gained less than expected gain.
55 Boys or 77% gained 2.27 times expected gain.	2 Boys gained average expected gain.	8 Boys gained less than expected gain.
53 Girls or 71% gained 2.1 times expected gain.	1 Girl gained average expected gain.	9 Girls gained less than expected gain.
108 Total or 74% gained 2.21 times expected gain.	3 Total or 2% gained average exp'd gain.	17 Total or 11% gained less than exp'd gain.

(Taking the expected gain for the period of observation, based on the annual gain for age.)

Number who increased in Height.

Boys.....	29
Girls.....	36
Total.....	65

or 41% showed increase in Height.

INDIVIDUAL GAINS IN WEIGHT AND HEIGHT.

	WEIGHT.			HEIGHT.	
Lbs.	Boys.	Girls.	Inches.	Boys.	Girls.
½ lb.....	7	3	½ in.....	8	2
1–2 "	16	13	1–2 "	7	10
2–3 "	12	12	2–3 "	6	7
3–4 "	9	9	3–4 "	5	..
4–5 "	5	9	4–5 "	1	10
5–6 "	3	7	5–6 "	2	4
6–7 "	7	1	6–8 "	..	3
7–8 "	1	2		29	36
8–9 "	1	1		or 40%	or 48%
9–10 "	..	2			
14– "	2	1			
15– "	..	1			
20– "	1	2			
23– "	1	..			
	65	68			

Total number of cases, 145—71 Boys; 74 Girls.
Period under observation, 1 to 6 months; average 3 months.

TABLE VI.—DISTRIBUTION OF GAIN IN WEIGHT AND INCREASE IN HEIGHT.

	Gained Weight. Girls.	Gained Weight. Boys.
Weight-Age Basis:		
Over Weight	3	4
Under Weight	33	36
Even Weight	27	25
Weight-Height Basis:		
Over Weight	7	8
Under Weight	35	36
Even Weight	20	21
	Increased in Height.	Increased in Height.
Height-Age Basis:		
Over Height	3	10
Under Height	8	8
Even Height	18	18

The results obtained in a dispensary class of patients must be far from ideal at best, yet our children did wonderfully well. The general impetus given the home and the child in the right direction is of far more value than the weight increase, although the latter is of great moment to mother and child.

Through the correction of physical defects having a bearing on the nutrition of the child, through the correction of home conditions, dietetic habits and hygiene, by education without monetary assistance, these results have been obtained.

How may this progress be prevented from being only temporary? It seems that here the school could play an important part. The great influence of the teacher especially among the poor, could be used to great advantage. The child of to-day, whatever his social position may be, usually gets what he asks for. The child who eats what is put before him, without question, is a rare find. Possibly through school lunches, where the habit of eating plain, building food in company with other children would create a wholesome appetite for it, a result could be obtained that would be permanent. Through the child the home would receive the education in food values and proper dietetic habits. Get the *child to demand the proper food* and the problem of undernourishment will be met more than half way.

The Alkali Reserve of the Blood in Various Diseases of the Skin

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HANS J. SCHWARTZ, M.D.
OSCAR L. LEVIN, M.D.
AND
H. C. MAHNKEN, M.D.
NEW YORK

THE ALKALI RESERVE OF THE BLOOD IN VARIOUS DISEASES OF THE SKIN*

HANS J. SCHWARTZ, M.D., OSCAR L. LEVIN, M.D.
AND
H. C. MAHNKEN, M.D.
NEW YORK

The alkali reserve, consisting of bicarbonates, alkali-protein compounds, and small quantities of alkali-phosphates, maintains the plasma at a constant slightly alkaline reaction despite the fact that acid products of metabolism are constantly being passed into the blood. Under normal conditions these substances are present in very constant quantities. A diminution in the alkali reserve is known as acidosis and may be recognized by a variety of clinical symptoms and by characteristic alterations in the composition of the blood, urine, and alveolar air.

ALKALINE REACTION OF PLASMA

Let us briefly consider how the slightly alkaline reaction of the plasma is maintained in the face of normal or abnormal acid production. As stated by Hawke, we must consider in this connection:

1. Sodium bicarbonate and carbon dioxid which are present in proper quantity to yield a nearly neutral reaction.

2. The acid monosodium hydrogen phosphate and the alkaline disodium hydrogen phosphate which also are present in proper proportion to yield a similar nearly neutral reaction.

3. The proteins which are amphoteric and therefore combine with acid or alkalies without change in reaction.

Acidosis, according to Van Slyke, is a condition in which the concentration of bicarbonate in the blood is reduced below the normal level. Lawrence Henderson defines acidosis as any disturbance of the acid-base equilibrium whereby the power to resist acids in the body is lost.

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* Read by title before the Forty-Second Annual Meeting of the American Dermatological Association, Atlantic City, June 16-18, 1919.

* From the Departments of Dermatology and Clinical Pathology, Cornell University Medical School and Laboratories of the Beth Israel Hospital.

Beneath all metabolism is a constant diminution of bicarbonate in the blood, and the main change in acidosis is the loss of blood bicarbonate. That this is a serious change can readily be understood in view of the fact that bicarbonate is the third constituent of the blood, water being first and salt second.

Carbon dioxid is being constantly formed in the tissues, is carried by the blood to the lungs, and eliminated as carbon dioxid. The blood is able to take up a quantity of the acid carbon dioxid without any appreciable change in reaction, and thus large amounts of acid are daily eliminated from the body. In this process the bicarbonate of the plasma plays an important part. The body fluids contain free carbonic acid in such amounts that it converts into bicarbonates all bases not bound by other acids. The bicarbonate of the blood represents exactly the excess of base left over after all the nonvolatile acids have been neutralized, and is available for neutralization of further acids. The acid products of metabolism may be volatile, like carbonic acid; or nonvolatile, like sulphuric acid, oxybutyric acid, etc.; the latter permanently unite with the reserve alkali of the blood, producing genuine acidosis. Thus the bicarbonate constitutes the alkali reserve of the body.

The sodium bicarbonate and disodium phosphate also react with acids, such as B-oxybutyric, lactic, etc., forming a sodium salt which is neutral in reaction, a monosodium phosphate which is slightly acid, and free carbonic acid. The carbonic acid and acid phosphate ionize to but a slight degree and therefore the hydrogen ion concentration of the blood is but slightly altered. The acid phosphate is rapidly eliminated by way of the urine, and the carbonic acid by way of the lungs.

BUFFER SUBSTANCES OF THE BLOOD

The sodium phosphate and sodium bicarbonate of the blood have been called "buffer substances" on account of their protective rôle in preventing pronounced changes in blood reaction after acid or alkali introduction. If large amounts of acid are continually poured into the blood these buffer substances decrease in amount and finally, when the body can no longer replace the destroyed buffers, acidosis results. Hence, acidosis is a lowering of the alkali reserve of the body. The depletion of the "buffer substances" lowers the power of the blood to carry carbonic acid, and if the depletion is sufficiently pronounced, carbonic acid accumulates in the tissues, stimulation of the respiratory center takes place, and thus gives rise to hyperpnea, one of the clinical symptoms of acidosis.

Acidosis is always secondary, arising during pathologic processes and influencing their course. It may be due to faulty absorption of

bases or to an unusual loss of bases from the body; to neutralization by abnormal amounts of acids, either normal or abnormal, or to the failure to eliminate acids. This increased amount of acids may be due to the production of abnormal acids or an overproduction of normal acids, either from ingestion of acids or of foods leading to an increased production of acids.

Acidosis may occur in diabetes mellitus, severe nephritis, in children's disorders—such as diarrhea, recurrent vomiting, food intoxication, etc. The acids known to be produced are acido-acetic acid and B-oxybutyric acid—these, with acetone, being classed as acetone bodies. Acidosis may also be produced in a normal person by proper changes in diet. A diet containing no carbohydrate will generally be followed within twenty-four hours by indication of acidosis. The feeding of a salt-free diet or a diet containing a large excess of acid-forming foods—such as meats, fish, eggs, and certain cereals—may also cause acidosis. In this case, however, the acidosis is not associated with the formation of acetone bodies.

DIAGNOSIS OF ACIDOSIS

A high urinary ammonia coefficient, though present in the majority of cases of acidosis, is not necessarily indicative of acidosis, as certain dietetic changes may produce a high urinary ammonia. Furthermore, fatal acidosis has been observed in uremia and in nutritional disorders of infants with no pronounced increase in the ammonia coefficient. Though one of the most characteristic features of acidosis is the production of abnormal quantities of acetone bodies, nevertheless, according to Hawke, "it is the consensus of the best opinion of the present time that acidosis can be best diagnosed and its course followed, not by the determination of acetone bodies in either urine or blood, but by the determination of certain other factors which are more or less typical of acidosis." These include the following:

1. *The Determination of the Alkali Tolerance of the Patient.*—This method is reliable in proving the absence of acidosis, but is not particularly reliable for showing either the presence or degree of acidosis when it exists. This is partly due to the fact that in conditions associated with acidosis the power of the kidneys for the excretion of alkalies may be markedly impaired.

2. *The Determination of the Carbon-Dioxid Tension of the Alveolar Air* (Fredericia's method, Marriott's method).—Because of the liability of error in the collection of the sample, and because of various other factors (psychical, etc.) which may influence the alveolar carbon dioxid tension beside the blood bicarbonate, this method is open to criticism. Nevertheless, it is of considerable value and has been widely adopted for clinical use.

3. *The Determination of the Hydrogen-Ion Concentration of the Blood.*—An increase in the hydrogen-ion concentration is only noted in cases of uncompensated acidosis. The various degrees of compensated acidosis cannot be diagnosed by a determination of the hydrogen-ion concentration; therefore its determination is of less value in the diagnosis of acidosis than the determination of the alkali reserve of the blood, the carbon dioxid tension of the alveolar air, or the alkali tolerance of the patient.

4. *The Determination of the Alkali Reserve of the Blood; Carbon Dioxid Capacity of the Plasma (Van Slyke and Cullen).*—This consists in saturating a given volume of blood plasma with carbon dioxid. A known quantity of the saturated plasma is then acidified within a suitable pipet and its carbon dioxid is liberated by the production of a partial vacuum. The liberated carbon dioxid is then placed under atmospheric pressure, its volume carefully measured, and the volume corresponding to 100 c.c. of plasma calculated. A decrease in the carbon dioxid indicates a depletion in the bicarbonate of the blood, and hence a *lowering* of the "alkali reserve."

The average normal value in the adult is 65 volumes per cent., with extreme limits of 80 to 53 volumes per cent. In mild acidosis with no pronounced symptoms we get values of 53 to 40 volumes per cent. Values of 30 to 40 volumes per cent. are obtained in cases of moderate to severe acidosis where symptoms may be apparent; and values below 30 volumes per cent. in severe acidosis with symptoms of acid intoxication. This is the method we have adopted in our work. In a small number of cases we have also used Marriott's method for determining the alkali reserve of the plasma—a modification of his method for determining the hydrogen-ion concentration of the blood. Parallel results were obtained with the two methods. All tests were done in duplicate, and in all cases the urine was examined for evidences of nephritis, diabetes mellitus, acetone bodies, etc., with negative results except in two cases of diabetes—one complicated by gangrene of the toes, the other by carbuncles.

In this work our attention has been almost entirely confined to the inflammatory dermatoses. On general principles it seemed more likely that an acidosis might be found associated with this group rather than with the dermatoses classed under the hypertrophies, atrophies, new growths, strictly parasitic affections, etc.

We have examined in all 139 cases, of which eighty, or 59.7 per cent., gave normal values; fifty, or 35.9 per cent., gave values indicating a mild acidosis; five, or 3.5 per cent., values indicating a moderate acidosis, and one, or 0.7 per cent., showed a severe acidosis. This last was in a case of diabetes complicated with carbuncles.

Diseases	Plasma Bicarbonate Carbon Dioxid Reduced to 0 Degrees 760 Mm. 80-53 Volume Per Cent. Normal, No. of Cases	53-40 Volume Per Cent. Mild Acidosis No. of Cases	40-30 Volume Per Cent. Moderate Acidosis No. of Cases	Below 30 Volume Per Cent. Severe Acidosis No. of Cases
Sycosis vulgaris (old cases)	3	2	..	..
Acne simplex	8	5	..	..
Acne indurata	3	2	1	..
Lichen planus	1	1	..	..
Psoriasis (moderate type)	5	0	..	..
Psoriasis (extensive)	1	7	..	..
Gangrene toes (diabetes)	—	—	1	..
Carbuncle (diabetes)	—	—	1	1
Scleroderma	1	1	..	..
Urticaria	4	4	..	..
Furunculosis	5	2	1	..
Pompholyx	1	1	..	..
Folliculitis	4	1	..	..
Impetigo contagiosa (severe)	—	1	..	..
Eczema—subacute	8	4	..	..
Eczema—chronic	17	10	..	..
Eczema—seborrheic (mild)	5	1	..	..
Eczema—seborrheic (severe)	1	4	..	..
Eczema—intertriginous	3	2	..	..
Dermatitis venenata	—	1	1	..
Pruritus vulvae	—	1	..	..
Purpura	1	..	..	..
Moeller's glossitis	1	..	..	..
Erythema nodosum	1	..	..	..
Von Recklinghausen's	1	..	..	..
Pityriasis rubra pilaris	1	..	..	..
Pityriasis rosea	1	..	..	..
Dermatitis herpetiformis	1	..	..	..
Erythema multiforme	2	..	..	..
Pruritus senilis	2	..	..	..
Lupus erythematosus	2	..	..	..

We realize that the number of examinations made is too small to warrant any definite conclusions being drawn, but we feel that a lowering of the alkali reserve has been found sufficiently frequently in acne, psoriasis, urticaria, furunculosis and eczema—particularly seborrheic eczema—to warrant further investigation.

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LICHEN ACUMINATUS

SAMUEL FELDMAN, M.D.
Attending Physician, Cornell Medical College Dispensary, Department of Dermatology; Assistant Dermatologist, Lebanon Hospital; Assistant Dermatologist, Fordham University
NEW YORK

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SAMUEL FELDMAN, M.D.
Attending Physician, Cornell Medical College Dispensary, Department of Dermatology; Assistant Dermatologist, Lebanon Hospital; Assistant Dermatologist, Fordham University
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INTRODUCTION

The rarity of lichen acuminatus and the opportunity to study a classic example of the disease induces the writer to submit the following recapitulation of the features of the dermatosis together with the report of a case and its histopathologic features.

Synonyms: Lichen ruber (Hebra), Pityriasis rubra pilaire (Dévèrgie), Lichen ruber acuminatus (Kaposi), Lichen acuminatus (Crocker).

History: This disease was first described by Claudius Tarral in 1828, but it remained unnamed until 1862, when Hebra described it under the name of lichen ruber. After that period it was reported under different names by various authors.

Onset: The eruption may be preceded by a febrile period with headache, chills and fever; by a shorter or longer period of pruritus or urticaria; by an acute circumscribed, patchy or diffuse erythema, edema or eczema; or the rash may appear without any prodromal symptoms.

Description of the Eruption: The papule is round at the base, conical or globular at the apex. Occasionally, grouped papules have the appearance of enlarged follicles, like cutis anserina. The papules vary in size from a small to a large pinhead. They may vary in the same individual, being larger on one part of the body than on another. They may be so small as to be visible only with a magnifying glass. The whole eruption may consist of white or chalky-white horny plugs, only slightly raised from the surface with little or no inflammatory areola. This last form is supposed to be characteristic of pityriasis rubra pilaris, but it is quite frequently present in lichen acuminatus, especially in early cases and also in old cases, occurring together with the larger papules.

The color varies from pink to rose, to light or dark, even bluish or brownish red. In the early stages it disappears on pressure, later it becomes more permanent. It may become obscured by scales and horny plugs.

The papules are dry, hard, rough and file-like and on passing a finger over them, they feel like a nutmeg grater. At times, the papules are thread-like or pointy as if chiseled off (Besnier); rarely they are soft, flattened and rounded (Kaposi).

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* From the Department of Dermatology, Cornell University Medical College.

The center of each papule is capped by a horny plug. The lanugo hair is usually invisible in the affected follicle. Occasionally it is broken off and it appears as a black dot at the apex of the horny plug. The latter pulls out very readily and may leave behind a lanugo hair in the center of a dark red or gray, often moist and rarely bleeding little pit, representing a dilated follicular opening.

Instead of plugs, there are occasionally furfuraceous or lamellar scales covering the papule. The resulting patch then resembles one of psoriasis. The color of the scales is either white, like gypsum, or whitish-gray, yellowish-white, grayish-yellow, sepia-brown or almost black. The scales may be fatty and resemble those of seborrhea (Kaposi).

The papule always retains its original size and never grows peripherally. Confluence never takes place. The disease spreads by formation of new papules which may become so crowded as to efface all intervening space, forming smaller or larger patches, which may assume any shape. On close examination, however, the origin of the lesion from a single papule can usually be disclosed, as there are always to be found discrete lesions about the patch. In some cases, when the infiltration of the interfollicular spaces raises the latter to the level of the follicle, the original primary lesion is not so easily recognized.

The resulting patch is thick, dry, rough and file-like. It is traversed by deep furrows and lines, and is covered with fine white scales. When the latter are removed the surface looks dark or bluish red, even violet and shiny. In some cases the patch is visibly elevated, rough and papillary. When the plugs are removed from a whole patch the surface looks like a sieve (Leukasievitz). Patches are never moist or crusty; never form vesicles or pustules and never ulcerate.

In comparatively early lesions the grouping of the papule follows the general distribution of the hair follicle. Some lesions are irregularly scattered, others appear in closely crowded groups, in circles, half circles, lines and rows, and point out the location of the follicle through their intimate relation with the hairs. As a rule, the eruption is bilateral and symmetrical. It may, however, be linear or unilateral (Hallopeau). At times, it follows the general localization of seborrhea (Wickham).

LOCALIZATION

The localization, in order of frequency, is as follows:

1. Extensor surfaces of the extremities; dorsal surfaces of the hands and fingers, especially first and second phalanges, in which locality the papules are arranged in circles and plainly indicate the grouping of the hair follicles; the extensor surfaces of the knees and elbows are often the seat of a layer of thick horny scales—"placards granites"—on a circumscribed red and infiltrated base.

2. On the palms and soles the eruption usually consists of a diffuse patch of hyperkeratosis, sharply marked off from the dorsal surface.

The papule may be discrete, conical or more or less flattened with horny plugs or whitish scales and resemble chalk drops, clavus, even verrucae.

3. The scalp and face may become early involved. On the scalp there is a diffuse redness, covered by white shiny scales, or seborrhea-like scales—"pityriasis capitis" (Dévèrgie).

4. Flexor surfaces of the extremities; on the torso.

5. Genitals; not present as constantly as in lichen planus and hence not as characteristic a site.

6. Papules quite commonly appear on the inner surfaces of the cheeks. There they are usually discrete, but may also form patches.

FORMS OF THE DISEASE

The description above given is that of the first stage of the disease and is known as *lichen acuminatus diffusus*. The eruption may remain for years localized to some regions of the body, or an originally widespread disease may recede and leave behind lesions limited to some places.

Lichen acuminatus universalis is the name applied to the disease when it has made further progress. The plaques become fused and cover the whole body. The skin is erythematous, deeply infiltrated and covered with fine scales. The natural lines become much exaggerated.

On the scalp the patches are red and are covered with thin lamellar scales or the latter may form one thick shield-like covering. The hair may remain normal or become thinned and atrophied and come away with the removal of the scales. Sometimes the hair, instead of falling, shows an abnormally thickened growth.

On the face the skin is thickened and deeply furrowed. The patient looks senile. The forehead may look leonine; the expression is altered. There may be difficulty in opening the mouth. The upper lids are lagophthalmic, the lower ectropic. Rhagades appear at the furrows of the nose and behind the ear. Eyebrows and eyelashes as well as hair from all regions of the body have a tendency to fall out. The joints of the fingers are stiffened in the form of a claw. Fissures which bleed and are extremely painful form about the flexor surfaces of the joints. Every motion leads to more cracks in the skin, causing severe pain.

The nails may present various forms of disturbances of nutrition; thickening, curving and fragmentation due to subungual hyerkeratoses. At times, there is an increased growth of the nails. The glands may become enlarged as in all itchy diseases.

Pityriasis rubra (Dévèrgie) is a secondary manifestation of the disease, which may mask the symptoms. There is a general erythema remaining for a long time without any thickening, but the skin becomes early covered with minute white scales. The surface looks velvety or shiny, like mother-of-pearl—Taylor's "alligator skin." In rare cases the erythema begins in the interfollicular spaces instead of in the

follicles. It may start as a pityriasis capitis, and it is therefore claimed that pityriasis rubra of the French authors is a separate disease. According to Jarisch, Heller, Rille and others, it is not impossible for scaliness of the scalp to be the first symptom noticed in lichen acuminatus.

Pityriasis palmaris (Dévèrgie) is applied to the disease when it begins as a general hyperkeratosis of the palms and soles.

GENERAL SYMPTOMS

In the diffuse form there are no symptoms excepting the itching. In the universal form the patient becomes bedridden on account of contracted joints, fissures of the skin and pain on motion. Extreme itching causes sleeplessness and nervousness. There is loss of flesh and the patient ends in marasmus.

Exacerbations and remissions are common. Acute cases may recede rapidly leaving lesions limited to some area or areas. The future course of the disease is not acute. Acute exacerbations may follow a chronic disease and vice-versa. The eruption may partly or wholly disappear, there being a remission for years. On the other hand, one eruption may follow rapidly after another.

This ability to recede is thought to be characteristic of pityriasis rubra pilaris, but it is known to occur also in lichen acuminatus.

When the lesion begins to heal the papule softens and becomes smaller, the color changes to a brownish or a dirty blue-red. This state of affairs may persist for a comparatively long time. The lesions finally disappear, leaving behind brown pigmentation and scaliness on a smooth surface, long after the papule has disappeared.

PROGNOSIS

The prognosis is generally favorable for life. Fatal cases occur more often in universal lichen planus than in severe pityriasis rubra, although fatal cases are not impossible in the latter disease, while in the former many cases recede and are influenced by treatment.

The cause of malignancy is the same as in other exfoliating dermatoses, namely, loss of heat by radiation, loss of albumin from exfoliation, neuroses from irritation and injury to the nerve endings.

COMPLICATIONS

Loss of hearing due to thickening of the ear canal. Ectropion and its complications such as pannus leading to blindness.

DIAGNOSIS

Relation of lichen acuminatus and pityriasis rubra pilaris to each other.

At present, almost all authors agree that the diseases are identical although a controversy as to their identity still exists. The two opinions are lined up as the identists, those that believe both diseases identical and the nonidentists.

Lichen Acuminatus	Pityriasis Rubra Pilaris
Non-Identists. Primary lesion always a papule; patches are secondary.	Patches are primary.
Identists. Primary erythema without papules on scalp, palms and soles.	
Non-Identists. Nodules are not constantly follicular, some are developed in the cutis. They never lack inflammatory signs. Hyperkeratosis is secondary.	Are always follicular. May lack all inflammatory signs and present only a horny plug. Lesions are primarily epidermic.
Identists.	Nodules are not always follicular They occur in the sweat gland ducts. Inflammation is present though mild. Both originate in the cutis.
Non-Identists. Predilection for the eruption is on the flexor surfaces.	On the extensor surfaces with symmetrical grouping on the first and second phalanges.
Identists.	(Above condition is found in both diseases.)
Non-Identists. The course is that of steady progress and is chronic.	Remissions and intermissions are characteristic.
Identists. This difference is denied.	
Non-Identists. Prognosis is poor.	Good.
Identists. Not all cases end fatally.	
Non-Identists. General health is poor.	Good.
Non-Identists. Arsenic influences the eruption favorably.	Does not influence.
The above described action of arsenic may be reversed.	
Non-Identists. Deep brown pigmentation.	Very slight or none at all.
Identists. Pigmentation is not constant or it may be due to arsenic treatment.	
Identists. Changes in the nails are the same. Both eruptions are frequent on the genitals.	

The weight of evidence seems to be on the side of the identists and all modern writers regard lichen acuminatus and pityriasis rubra pilaris as different names for the same disease.

Relation of lichen acuminatus and lichen planus to each other.

There are very many points of resemblance between the two conditions.

1. It is now an undisputed fact that both diseases may be present in the same patient. Lichen acuminatus papules are frequently found on lichen planus patients (Jadassohn, Riecke).

2. Both diseases may start with a general flat inflammation as hyperemia, erythema, eczema.

3. Transitions from one disease to the other may occur.

4. Each succeeding attack may change from one to the other disease.

5. Arsenic is helpful in both.

6. Variations of one disease may also be found in the other, as follows:

Lichen Ruber Acuminatus Verrucosus et Reticularis: This condition consists of ridges composed of rows of single papules. The ridges are elevated from the surface and resemble a keloid or hypertrophic scar. They run parallel to the long axis of the body or cross each other to form a network. The color is sepia brown.

Moniliform Lichen Acuminatus (Kaposi): This is a condition produced when deepened natural lines divide up the ridges above described and with the sepia brown color may resemble strings of coral.

These two conditions may be found in both diseases, only in lichen acuminatus the surface is rough and file-like, while in lichen planus the surface is smooth and waxy. Both forms of moniliform lichen may coexist.

Lichen planus comedo has a waxy, shiny papule with a black comedo-like body resembling the black props found in lichen acuminatus, only the latter papule is red and pointy. Both forms are rough and file-like. They may be found isolated without any other secondary lesions.

Lichen Ruber Verrucosus et Follicularis "en corymbe" (Jadassohn): The arrangement resembles a similar condition frequently seen in syphilis, corymbiform syphilid, small papules grouping themselves around a larger papule or patch. The papules themselves are either comedo-like bodies with blackheads set in flat follicular papules, or red acuminate papules with blackheads (Lavargue, Hallopeau). This condition is found with equal frequency in both diseases.

DIFFERENTIAL DIAGNOSIS

Differentiation Between Lichen Acuminatus and Lichen Pilaris [Keratosis pilaris alba et rubra (Brocq). Xeroderma pilaire erythemataux (Besnier). Keratosis pilaris*]

Lichen Acuminatus	Lichen Pilaris
Onset: Acute.	Very insidious.
Location: Common on the flexor surfaces of joints. Typical location, back of the first and second phalanges.	Extensor surfaces of extremities and buttocks, less on the flexor surfaces but never about the joints.
Grouping: Occurs in groups, lines, circles, figures and patches.	Disseminated. No grouping, no patches.
Scalp: Involved.	Never involved. The disease occurs only about the lanugo hair.
Remissions and Exacerbations: These are the rule.	Never occur. Course is steady and chronic.
Hair: It may involve any hair follicle.	Always a lanugo hair which becomes coiled up and covered by a scale.
Color: Color of the papule is red or brown.	Nearly normal or dirty gray.

When keratosis pilaris is strongly developed it resembles lichen acuminatus. When the palms and soles are involved the diagnosis is still more difficult.

Microscopic Diagnosis. — The two conditions are very similar. Unna gives the following characteristic differences:

1. The keratosis in keratosis pilaris is distinctly limited to the follicle and does not involve the neighboring corneal layer as is the case in lichen acuminatus.

2. The mouth of the follicle is cylindrically dilated. The follicle itself is deformed and pushed to one side together with the hair, which is spirally twisted. The appendages are intact. In lichen acuminatus the enlargement of the follicular opening is crater-like, is filled with a plug which may or may not be pierced by a normal or broken off hair.

3. Marked infiltration of the cutis with intercellular edema is always present in lichen acuminatus and is normally absent in keratosis pilaris, although mild cell infiltration may sometimes be found.

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* In discussing the differential diagnosis the synonyms of each disease will, as far as possible, be enumerated, as the nomenclature of many of the conditions in question is not at all clear.

Macroscopic Diagnosis.—Keratosis pilaris rubra (Brocq) can be distinguished by its occurrence in young neurotic women and children, and in families with ichthyosis, by its localization on the arms and buttocks; by the bluish marbled appearance of the skin, the bluish-red, very minute papules, by the color being due to hyperemia and hence being influenced by pressure, temperature and circulation; and by areas of atrophy found in the older lesions.

Ichthyosis follicularis (Lesser): The occurrence in early life; the absence of all inflammatory signs, and the scale being attached in the center with free and rolled-up edges, should make the diagnosis certain.

Keratosis follicularis contagiosa (Brook): Acne sebacea cornea (Cazenave). Acne cornée (Leloir and Vidal). Ichthyosis sebacea cornea (Wilson). This disease begins as a black point, comedo-like, and develops into a deeply pigmented papule. In lichen acuminatus the papule is the first to appear, its black point is a broken-off hair or a pigmented plug and appears later. The skin between the papules is normal in lichen acuminatus, while in this disease each papule is surrounded by an inflammatory areola. The plugs are black and very firmly adherent. They project a wedge into the papule, and when they are pulled out, will rattle like metallic fragments on a piece of paper. In lichen acuminatus the plug is gray and comes out very easily. There is very much pigmentation. The lesions look dirty. Microscopically, keratosis follicularis contagiosa is a hyperkeratosis and parakeratosis of the hair follicle and sebaceous follicle and the sweat duct, presenting cell changes similar to those of Darier's disease and may be identical with it. Finally, the course is different in both diseases.

Psorospermosis follicularis vegetans: Keratosis follicularis vegetans. Darier's disease. The color of the primary papule is yellowish-gray and not much different from the normal skin; no inflammatory signs. The lesion resembles keratosis pilaris. The later papule is greasy-looking and brown in color with a greasy or dry plug which breaks off easily, and when removed leaves a bleeding crater (Kaposi). Localization, generalized. The lesions are rough and they crack and become purulent. The plugs are large, yellowish horny masses.

Lichen spinulosus (Dévêrgie): Lichen pilaris seu spinulosus (Crocker). The lesions in this disease are both macroscopically and microscopically almost identical with lichen acuminatus. The differences are: that the lesions come on in rapid succession of crops almost over night; its common location is on the back of the neck and buttocks and never occurs on the face or hands; and it occurs in early life.

Lichen scrophulosorum: The important differences are: very slow onset. It occurs in children with tuberculous tendency. The lesions

are a mixture of both acuminate and flat angular papules. Patches form by coalescence. Secondary lesions: vesicles, pustules, eczema are usually present. It never occurs on the genitals. Under the microscope the structure of a tubercle is readily made out.

Lichen nitidus: This rare disease can hardly be confused with lichen acuminatus. It rather resembles lichen scrofulosorum. The lesions are similar in shape and color to the flat variety of papules in the latter disease; there is a complete absence of itching and constitutional symptoms; it is chronic and stationary. Under the microscope the structure is that of a tubercle.

Lichen lividus (Wilan) is found on the legs of old people and during the course of lichen scrofulosorum. The lesion consists of a hemorrhagic papule.

Lichen syphiliticus at a glance, presents a picture very similar to lichen acuminatus. There is the same papule, only a little paler or yellowish, with its horny plug which does not pull out as readily as in lichen acuminatus. The papules, however, are very numerous and closely packed, and are symmetrically distributed. Their presence on the face, to the hair line, is very striking. They may be preceded by macules. Finally, the history of the case and the presence of associated lesions, as pustules, etc., ought to make the diagnosis certain.

Tertiary papular syphilid resembles lichen acuminatus by its grouping in lines, circles, etc., but its localization, the presence of associated lesions and the history of the case will help the differential diagnosis.

Psoriasis can be mistaken only for universal lichen acuminatus, but the adherent scales which leave bleeding points when removed, the absolutely smooth surface under the scales and the absence of discrete acuminate papules at the border, make the distinction easy.

Psoriasis palmaris et plantaris occurs late in psoriasis, and only in very severe cases; in lichen acuminatus palmar and plantar lesions may be the first symptoms. There is also less swelling in psoriasis, and the edges are less sharply outlined.

General exfoliating erythrodermia: It may be impossible to distinguish this condition from universal lichen acuminatus. A careful search must be made for discrete papules and the history must be taken into consideration.

Prurigo: The papule is relatively soft without horny plugs. It occurs mainly on the extensor surfaces of the extremities and is of comparatively short duration.

Papular eczema should not be confused with this disease. The papule is soft and there are associated lesions present.

Tar, chrysarobin and pyrogallol rashes: A comedo-like body capping a papule bears some resemblance to the disease in question, but the history of the case and the inflammatory symptoms will make a mistake impossible.

ETIOLOGY OF LICHEN ACUMINATUS

The cause of this disease is unknown. Intestinal putrefaction may cause a weakened resistance against the real causative factor or may generate the latter. Deterioration of the general health is provocative. In the same way nervous strain, worry and fear may be contributing causes. Exacerbations of the disease occur during periods of body depression (Cunningham).

HISTOPATHOLOGY

There is no difference in opinion as to the hyperkeratosis; but writers differ as to whether the infiltration of the cutis is primary or secondary.

Stratum Corneum: There is a general hyerkeratosis, the horny layer is increased from two to ten times. It is composed of wavy, homogeneous, lamellar layers. There is but rarely any parakeratosis, only occasionally a nucleated horny cell can be found, and that at the base only. Conical, globular or cylindrical masses project into the hair follicle, forming the plug. The latter is composed of concentrically arranged lamellar layers, like an onion. The lanugo hair may be retained in the mass, or it may have fallen out and an oblong space is found corresponding to it. The plug may become so large as to pull down the surface skin with it; in that manner two follicles may unite to form a twin follicle. There are two other locations where a plug can be formed, namely, in the sweat gland duct and in the rete pegs. A marked hyperkeratosis and plug formation has been observed in the sweat gland duct, which occasionally leads to sweat gland cysts by occlusion of the outlet. Cornification and horny plug formation also may take place in some of the rete pegs.

The rete malpighii is hypertrophied. The cells of the rete may show slight changes, the nuclei are large, vesicular and separated from the protoplasm. The basal layer may be increased in thickness or it may be missing, and between the cells of the rete malpighii and the corneum there is a space filled with round cells, leukocytes and detritus. The whole process is due to edema.

Papillary Layer: In the early stage, there is vascular dilatation and perivascular infiltration in the papillae leading downward even to the subcutis. In the second stage the infiltration becomes diffuse. In severe cases the infiltration may extend into the epithelial layer. In

the third stage the diffuse character is lost and the infiltration is localized about the hair follicle, also about the sweat and sebaceous glands to a lesser extent.

Character of the Cells: (*a*) Mononuclear leukocytes. (*b*) Large spindle-shaped fibroblasts. (*c*) Few plasma cells. (*d*) A fairly large number of mast cells.

Arrectores pilorum are hypertrophied. Fibrous, elastic and nerve tissues are normal.

REPORT OF CASE

History.—S. R., aged 40, a moving picture operator, came to the Cornell Dispensary, Jan. 16, 1916.

He stated that in June, 1915, large red blotches appeared in his groins and spread to the back, the abdomen and the chest. Simultaneously with the eruption there came an intense itching. The latter appeared rather suddenly. The itching was most intense in places where parts come in contact with each other and where perspiration is more profuse, as in the groins, axillae and about the scrotum.

He does not remember having had any fever. As to headaches, nothing definite can be stated, as at the time of the onset of the disease the patient was a chronic sufferer from headaches.

The blotches remained stationary for about a month, then they gradually subsided. The itching at that time was still as intense as at the start. Gradually little black "pimples" like blackheads began to appear. Among them were red "pimples" like prickly heat.

The rash first appeared in the groins and about the hips and from there it continually spread upward and only very little downward. About December, 1915, the patient states, the skin began to feel rough and look dirty. The itching was still as intense as before.

Status Praesens (Jan. 16, 1916).—There is a discrete papular eruption covering the entire abdomen, the chest to just above the nipple line, the back, both buttocks and a belt of very thickly crowded papules about the waist line. The eruption extends downward on the posterior surfaces of both thighs to about the junction of the middle and lower third. The papules are less numerous on the anterior surfaces of the thighs and become still fewer as the eruption extends downward. Below the middle of the thigh there is not a single papule to be seen. There are several discrete papules on the glans penis and on the prepuce. Posteriorly, the eruption extends upward to the seventh cervical vertebra, over both scapular regions, both deltoids and down on the extensor surfaces of the arms, forearms, wrists, hands and fingers. The papules are especially prominent on the first and second phalanges where they are arranged in parallel rows. On the flexor surfaces of the arm the lesions are fewer and none is seen on the flexor surfaces of the forearms, hands and fingers. On the inner surfaces of both cheeks, about half a dozen papules can be found. They are discrete, gray in color and are indistinguishable from those of lichen planus.

The distribution is strikingly symmetrical. If there is a patch of very closely crowded papules in any region on one side of the body, there is a correspondng one on the opposite side. Similarly, when the papules are only sparingly present or are entirely absent from a place on one side of the body, the same will be true of the corresponding place on the opposite side. Most of the papules are diffusely scattered without arrangement, but a number appear in larger and smaller groups or form straight and curved lines, circles and segments of circles. On the backs of the first and second phalanges the papules are arranged in straight parallel rows.

The size of the papule is variable, averaging about the size of a large pinhead, and most of them are well raised above the surface.

The papules vary from red to purple in color. A small number are yellowish-brown. They are tough to the touch and a rough, gray, horny plug projects from the apex of nearly every papule. The plugs are up to 2 mm. in length; they can be pulled out quite readily and on removal leave a red, shiny depression in the center of the lesion. Some plugs are shorter and stubbier and brown to almost black in color. On a number of lesions the plug is so tiny that it can hardly be seen, but it can be felt quite readily with the finger. A smaller number lack the plugs entirely and only a slight fine scaliness can be seen to cap the top of each papule. Finally several papules have no plugs and no scales, the color being that of normal skin. The lesion as a whole resembles goose-skin.

General Symptoms.—Outside of the itching there is only a slight pallor. The pulse is 76, normal, full and compressible.

Blood Examination, Jan. 18, 1916: hemoglobin, 84 per cent.; white blood cells and differential count, normal.

Treatment.—The patient was given $\frac{1}{40}$ grain Asiatic pills, was instructed to take one pill three times a day and to increase the dose gradually until ten pills per day were reached. Local Treatment: The only drug used was ammoniated mercury, 5 per cent. in ointment form, applied once daily.

Biopsy.—This was made on the above date. Specimens were stained with hematoxylin-eosin; polychrome-orcein; von Pappenheim; safranin-wasserblau; dahlia; picro-lithio-carmine; picro-nigrocin; and hematoxylin-Delafield.

Pathologic Findings.—The corneal layer is much thickened and appears in homogeneous, wavy, superimposed lamellae. No parakeratotic cells are to be found. The stratum lucidum cannot be made out. The stratum granulosum is apparently normal. Stratum malpighii is thickened. The rete pegs are not elongated but are thickened. The basal layer is normal.

The hair follicle is widely dilated, more so toward its mouth. A horny mass fills out the cavity and it contains in its center an unaltered hair. The horny mass is arranged in longitudinal concentric lamellae, except for the deepest portion where the arrangement is more or less horizontal and the outline of the horny cells is distinctly retained.

The stratum granulosum of the follicle appears to be coarser and in some places the granules run together in large fat-like droplets.

The rete appears thinner in places and thicker in others.

The basal layer is thickened in places and in others is thinned or missing, being obscured by the round cell infiltration into the epithelial layer. In one place there is a large space between what appears to be the rete and the infiltrate surrounding the follicle, the basal layer being completely absent.

Throughout the whole corium and more so in the upper layer there are to be seen long rows and circles of round cell infiltrations, indicating the presence of a perivascular localization. The latter is more marked about the dilated follicle and also the sweat glands.

The fibrous sheath of the follicle is thickly infiltrated; the infiltration extends quite a distance out into the corium.

Cells composing the infiltrate: mononuclear leukocytes, large spindle-shaped fibroblasts, plasma cells, few in number, and comparatively many mast cells. Mitotic figures were only rarely observed.

Progress of the Condition and Results of Treatment.—March 8, 1916: The itching is much improved. Some papules can be seen to be involuting. They are smaller and paler. There are fewer papules on the backs of the fingers than there were on the previous visit.

March 22, 1916: No further improvement is noticed. Treatment is continued.

April 13, 1916: There is some slight improvement in both the itching and the appearance of the papules. The arsenic treatment was continued but the local treatment was changed to 5 per cent. oleum rusci in Lassar's paste.

A second biopsy was made. The section was taken from the back and a spot selected where the papules had the color of the normal skin, to determine the presence of infiltration. The section passed through two papules, one cut transversely and the other longitudinally. The latter was a double follicle filled with a bifurcated plug. Although the papules selected were indistinguishable from the normal skin, the infiltration was as marked as in the specimen from the first biopsy. Neither of these papules contained a hair.

May 24, 1916: There is marked improvement. There is still a number of deep red papules, raised above the surface and capped with long horny plugs. Most of the lesions, however, are smaller; the color is dirty gray, pink or yellowish-brown. The papule is capped with an almost flat, black, horny plug, not unlike a comedo. A large number of papules are normal in color and possesses no plug.

Scattered among the other papules and especially numerous in the groins and axillae, there are deep red papules of the size of a sago seed. They present at the apex a grayish white mass, resembling a pustule. The whole lesion resembles a pustular acne. Embedded in the pustule-like apex of the papule is a horny plug, which comes out with the slightest scratching with the finger nail and leaves behind a deep crater-like, gaping, moist and shiny depression. No pus, however, can be detected. The origin of the above described lesion may be that some involuting papules are influenced by heat and moisture and also by irritation from scratching. When a plug is pulled out of a small colorless papule, the latter turns pink in color, becomes almost flat and has in its center a small punched-out cavity. If the same operation is performed on a number of closely packed papules, the surface looks honeycombed.

A third biopsy was taken. Now lesions were selected that had no visible horny plugs and as a whole looked like goose skin. There were two papules in the field, both cut transversely. From one the plug had fallen out and left a cavity in its place, the other contained a small plug without a lanugo hair. Infiltration was present, though in less marked degree than in the previous sections.

May 27, 1916: Improvement is rapid. Most of the lesions are entirely flat. The keratotic plugs are black and only slightly project from a nearly normal surface. They come out with the slightest scratching over the surface with the finger nails and leave a very minute normally colored dimple behind them. Other papules are in various stages of involution. Arsenic treatment is discontinued; the local treatment is still kept up.

June 23, 1916: The lesions have almost entirely disappeared and only scattered here and there are individual papules and groups of papules in various stages of involution. There are many large, brown pigmented patches over the shoulders, arms and the back; also in the form of a belt around the waist, in other words, in all locations where the lesions were most numerous.

Scattered all over the body, but comparatively few in number, are horny plugs on an almost flat, slightly brownish surface. The plugs are indistinguishable from comedones at first glance; only when scratched out from their site does the difference become evident. They are hard and short horny masses. The lesions in the mouth are about half their former size, but are still present and distinct.

Jan. 22, 1918: The skin is entirely soft and smooth. It is entirely free of any eruption. Patches of pigmentation, however, are still present, especially about the waist line.

March 19, 1918: Pigmentation is still present.

July 7, 1918: Pigmentation has not entirely disappeared.

SUMMARY

The points of importance presented by this patient are:

1. The onset with a preceding erythema; the absolute benignity of the disease; the typical location on the backs of the first and second phalanges pointing to pityriasis rubra pilaris; the constant presence of infiltration; the presence of a plug without any signs of hair structure; the long intermission — nearly three years; the rapid improvement under arsenic treatment pointing clearly to lichen acuminatus. From the above it seems certain that the two diseases in question are identical.

2. The presence of the eruption in the mouth and the response to arsenic treatment links it closely to lichen planus.

909 Kelly Street.

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